(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 114126620 B
(45)授权公告日 2024.12.31

(21)申请号 202080035916.4

(22)申请日 2020.05.12

(65)同一申请的已公布的文献号
申请公布号 CN 114126620 A

(43)申请公布日 2022.03.01

(30)优先权数据
62/846,991 2019.05.13 US
62/993,957 2020.03.24 US
63/011,469 2020.04.17 US

(85)PCT国际申请进入国家阶段日
2021.11.12

(86)PCT国际申请的申请数据
PCT/US2020/032474 2020.05.12

(87)PCT国际申请的公布数据
WO2020/231990 EN 2020.11.19

(73)专利权人 传达治疗有限公司
地址 美国马萨诸塞州
专利权人 D.E.萧尔研究有限公司

(72)发明人 B-B·托雷 H·舍恩赫尔
A·M·泰勒 F·焦尔达内途
D·T·慕斯塔卡斯
T·H·麦克莱恩 B·M·赫德森
M·M·梅德 P·阿亚兹
D·A·沙龙 R·库鲁库拉苏里亚
A·博齐奥

(74)专利代理机构 北京律盟知识产权代理有限责任公司 11287
专利代理师 奚勇

(51)Int.Cl.
C07D 487/04(2006.01)
A61K 31/519(2006.01)

(56)对比文件
WO 2006004703 A2,2006.01.12
WO 2005121147 A1,2005.12.22
WO 02100864 A1,2002.12.19
WO 2006004658 A2,2006.01.12
WO 2007079862 A1,2007.07.19
EP 3269370 A1,2018.01.17
CN 103958512 A,2014.07.30
Géraldine Calvet,等."Synthesis of Polysubstituted 5-Azaindoles via Palladium-Catalyzed Heteroannulation of Diarylalkynes".《The Journal of Organic Chemistry》.2011,第76卷(第11期),第4376页表3、表4.

审查员 唐淋

权利要求书1页 说明书870页

(54)发明名称

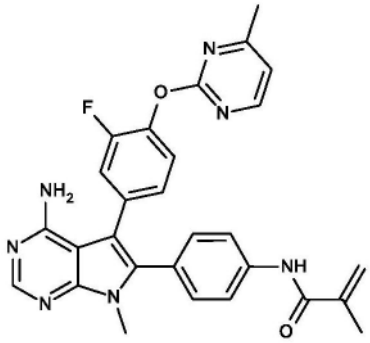
FGFR抑制剂和其使用方法

(57)摘要

本公开涉及新颖化合物和其医药组合物以及使用本发明的所述化合物和组合物抑制FGFR酶活性的方法。本公开进一步涉及但不限于使用本发明的所述化合物和组合物治疗与FGFR信号传导有关的病症的方法。

CN 114126620 B

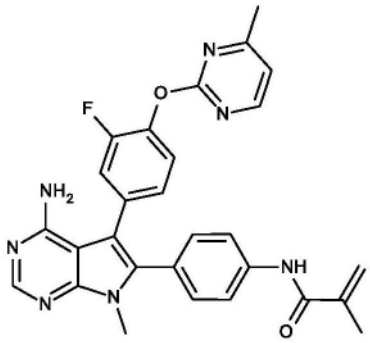
1.一种化合物,其是



,

或其医药学上可接受的盐。

2.一种医药组合物,其包括化合物:



,

或其医药学上可接受的盐以及医药学上可接受的载剂、佐剂或媒剂。

3.一种根据权利要求1所述的化合物或其医药学上可接受的盐或根据权利要求2所述的医药组合物在制备用于抑制有需要的个体中的FGFR2信号传导活性的药物中的用途。

4.一种根据权利要求1所述的化合物或其医药学上可接受的盐或根据权利要求2所述的医药组合物在制备用于治疗有需要的个体的FGFR2介导性病症的药物中的用途。

5.一种根据权利要求1所述的化合物或其医药学上可接受的盐或根据权利要求2所述的医药组合物在制备用于治疗个体的病症的药物中的用途,其中所述病症是胆管癌、肝癌、乳癌、前列腺癌、肺癌、甲状腺癌、胃癌、卵巢癌、直肠癌、子宫内膜癌或尿道上皮癌。

6.根据权利要求5所述的用途,其中所述病症是胆管癌。

7.根据权利要求6所述的用途,其中所述胆管癌为肝内胆管癌。

8.根据权利要求5所述的用途,其中所述病症是肝癌。

9.根据权利要求8所述的用途,其中所述肝癌为肝细胞癌。

10.根据权利要求5所述的用途,其中所述病症是肺癌。

11.根据权利要求10所述的用途,其中所述肺癌是肺鳞状细胞癌或非小细胞肺癌。

FGFR抑制剂和其使用方法

[0001] 相关申请的交叉参考

[0002] 本申请要求2019年5月13日提交的美国临时申请第62/846,991号、2020年3月24日提交的美国临时申请第62/993,957号;及2020年4月17日提交的美国临时申请第63/011,469号的权益,所述美国临时申请各自以引用的方式并入本文中。

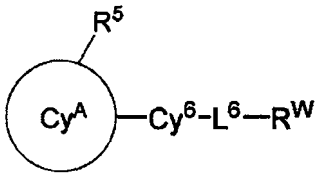
背景技术

[0003] 纤维母细胞生长因子受体(FGFR1、FGFR2、FGFR3和FGFR4)是由细胞外配体结合域和细胞内酪氨酸激酶域组成的受体酪氨酸激酶。FGF配体的结合引起受体二聚合和胞内域构形变化,从而引起激酶域和细胞内尾部发生分子间转磷酸化。磷酸化残基充当接附蛋白的对接位点,其促进下游信号级联,从而产生细胞行为,包括增殖、存活、分化、迁移和血管生成。失调的FGFR信号传导可经由以下发生:FGFR基因扩增或融合、FGFR错义突变、由表观遗传和/或转录调控因子的调节异常引起的受体过度表达,或FGF配体在肿瘤微环境中的上调。FGFR表达于许多细胞类型中;因此,异常的FGFR信号传导已牵涉到许多肿瘤类型的瘤形成、肿瘤恶化及对治疗的抗性。(关于FGFR信号传导的综述,参见N.特勒(N.Turner)及R.格罗斯(R.Grose),《自然·综述·癌症(Nat.Rev.Cancer)》2010,10:116-129;及其中引用的参考文献)。

[0004] 泛FGFR1-3抑制剂已对FGFR改变的多种癌症产生临床应答,然而,在靶毒性限制这些抑制剂的施用。泛FGFR抑制的最常见副作用之一是高磷酸盐血症。磷酸盐再吸收的调控是由FGFR3和FGFR1介导。因此,需要不伤害FGFR1的FGFR选择性抑制剂。(J.加替勒尼(J.Gattineni)等人,《美国生理学杂志·肾脏生理学(Am.J.Physiol.Renal Physiol.)》2014,306:F351-F358;X.韩(X.Han)等人,PLoS One 2016,11:e0147845.)。含有FGFR2基因融合体的癌症以及具有FGFR2扩增和/或FGFR2活化突变的癌症已对泛FGFR抑制展现应答,然而,低应答速率和持续时间表明其受到毒性限制。因此,需要FGFR2选择性抑制剂化合物及用这些化合物治疗癌症和其它病症的方法。(关于泛FGFR1-3抑制剂及临床应答的评述,参见I.S.巴必娜(I.S.Babina)及N.C.特勒(N.C.Turner),《自然·综述·癌症(Nat.Rev.Cancer)》2017,17:318-332;M.卡托(M.Katoh),《自然·综述·临床肿瘤学(Nat.Rev.Clin.Oncol.)》2019,16:105-122;及其中引用的参考文献)。

发明内容

[0005] 在一些实施例中,本公开提供式I-1化合物:

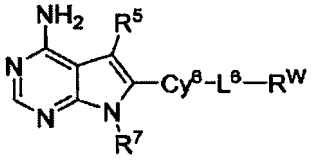
[0006] 

I-1

[0007] 或其药学上可接受的盐,其中Cy^A、Cy^6、L^6、R^5及R^W中的每一者如本文实施例及各类

别及子类中所定义。

[0008] 在一些实施例中,本发明提供式I化合物:

[0009] 

I

[0010] 或其药学上可接受的盐,其中Cy^6、L^6、R^5、R^7及R^W中的每一者如本文实施例以及各类别及子类中所定义。

[0011] 在一些实施例中,本公开提供一种医药组合物,其包含式I化合物或其药学上可接受的盐及药学上可接受的载剂、佐剂或稀释剂。在一些实施例中,本发明提供一种医药组合物,其包含本公开的化合物,例如式I-1化合物或其药学上可接受的盐,以及药学上可接受的载剂、佐剂或稀释剂。

[0012] 在一些实施例中,本发明提供一种治疗FGFR介导性病症的方法,包含向有需要的患者施用式I化合物或包含所述化合物的组合物。在一些实施例中,本发明提供一种治疗FGFR介导性病症的方法,包含向有需要的患者施用本公开的化合物,例如式I-1化合物,或包含所述化合物的组合物。

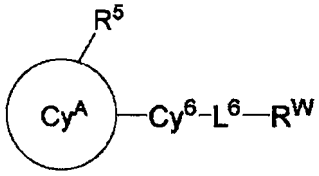
[0013] 在一些实施例中,本发明提供一种用于提供式I化合物或其合成中间物的方法。在一些实施例中,本发明提供一种用于提供本公开的化合物(例如式I-1化合物)或其合成中间物的方法。

[0014] 在一些实施例中,本发明提供一种用于提供包含式I化合物的医药组合物的方法。在一些实施例中,本发明提供一种用于提供包含本公开的化合物(例如式I-1化合物)的医药组合物的方法。

具体实施方式

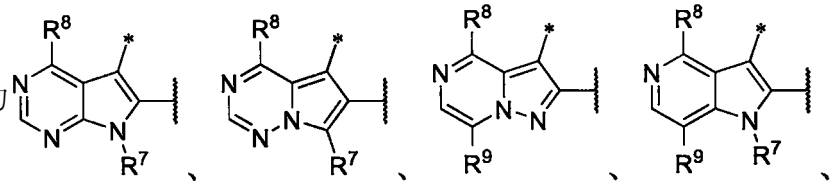
[0015] 1.本发明的某些实施例的一般描述

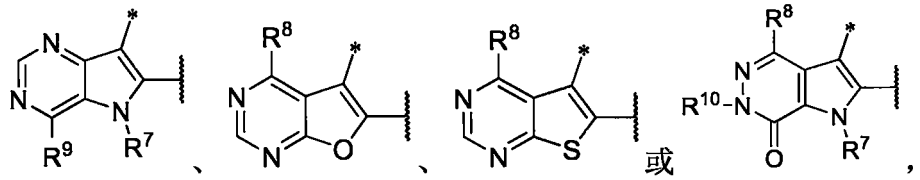
[0016] 本发明化合物及其医药组合物适用作FGFR2抑制剂。在一些实施例中,本发明提供一种式I-1化合物:

[0017] 

I-1

[0018] 或其药学上可接受的盐,其中:

[0019] Cy^A为 



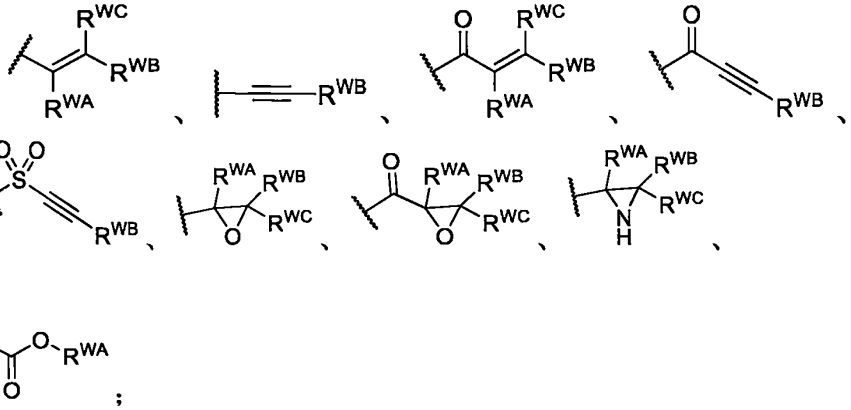
[0020] 其中表示连至R^5之键结且表示连至Cy^6之键结；

[0021] R^5为$-R^{5A}-L^5-R^{5B}$；

[0022] R^{5A}为R^B之二价基团，其中除$-L^5-R^{5B}$之外，R^{5A}还经m个R^{5C}实例取代；

[0023] R^{5B}为氢或R^B，其中R^{5B}经n个R^{5D}实例取代；

[0024] Cy^6为亚苯基；3至14元饱和或部分不饱和二价碳环；具有1至4个独立地选自氮、氧及硫的杂原子的3至14元饱和或部分不饱和二价杂环；或具有1至4个独立地选自氮、氧及硫的杂原子的5至14元亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代；

[0025] R^W是卤素、-CN、 

[0026] R^6的各实例独立地是R^A或R^B，其中R^6经q个R^C实例取代；或

[0027] 两个R^6实例、一个R^6实例及一个R^L实例、一个R^6实例及一个R^{WA}实例，或一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至8元部分不饱和或芳香族环；其中所述环经r个R^C实例取代；

[0028] R^7是H或R^B，其中R^7经t个R^{7A}实例取代；

[0029] R^8是H、$-NR_2$、卤素、-OH，或任选地经1至3个卤素取代的C_{1-6}脂肪族；

[0030] R^9是H、$-NR_2$、卤素，或任选地经1至3个卤素取代的C_{1-6}脂肪族；

[0031] R^{10}是H或任选地经1至3个卤素取代的C_{1-6}脂肪族；

[0032] L^5及L^6中的每一者独立地是共价键，或C_{1-4}饱和或不饱和、直链或分支链二价烃链，其中所述链中的一或两个亚甲基单元任选地且独立地经以下置换：$-CH(R^L)-$、$-C(R^L)_2-$、C_{3-6}亚环烷基、3至6元亚杂环烷基、5至6元亚杂芳基、-NH-、$-N(R^L)-$、$-NHC(O)-$、$-N(R^L)C(O)-$、$-C(O)NH-$、$-C(O)N(R^L)-$、$-NHS(O)_2-$、$-N(R^L)S(O)_2-$、$-S(O)_2NH-$、$-S(O)_2N(R^L)-$、-O-、-C(O)-、-OC(O)-、$-C(O)O-$、-S-、-S(O)-或$-S(O)_2-$；其中所述C_{3-6}亚环烷基、3至6元亚杂环烷基及5至6元亚杂芳基中的每一者任选地经一个R^A或C_{1-6}脂肪族实例取代；

[0033] R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘、卤素、-CN、-C(O)R、-C(O)OR、$-C(O)NR_2$、-C(O)N(R)OR，或选自以下的任选地经取代的基团：C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环，及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环；或

[0034] R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例，或R^{WC}及一个R^L实例与其间插原子一起形成具

有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环;其中所述环经w个R^C实例取代;

[0035] R^{WD}是卤素或-OS(O)$_2$R;

[0036] R^{5C}、R^{5D}、R^{7A}及R^L的各实例独立地是R^A或R^B,且经u个R^C实例取代;或

[0037] 两个R^{5C}实例、一个R^{5C}实例及一个R^{5D}实例,或两个R^{5D}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的3至7元饱和、部分不饱和或芳香族环;其中所述环经v个R^C实例取代;

[0038] R^A的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$或-N(R)S(O)$_2$R;

[0039] R^B的各实例独立地是C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;或具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环;

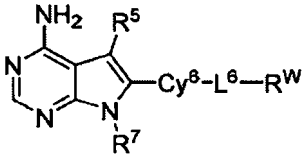
[0040] R^C的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-S(O)$_2$F、-OS(O)$_2$F、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R,或选自以下的任选地经取代的基团:$C_{1-6}$脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;

[0041] 各R独立地是氢或选自以下的任选地经取代的基团:C_{1-6}脂肪族;苯基;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环;及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环,或:

[0042] 同一氮上的两个R基团与其间插原子一起形成4至7元饱和、部分不饱和或杂芳基环,除所述氮之外,所述杂芳基环还具有0至3个独立地选自氮、氧及硫的杂原子;

[0043] m、n、p、q、r、t、u、v及w中的每一者独立地是0、1、2、3或4。

[0044] 在一些实施例中,本发明提供一种式I化合物:

[0045] 

I

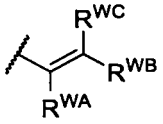
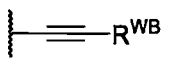
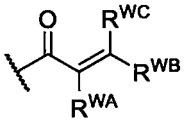
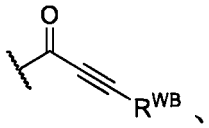
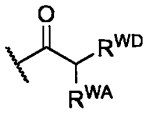
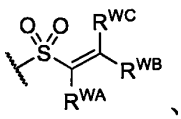
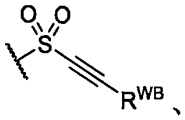
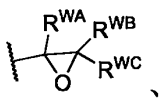
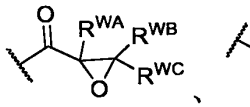
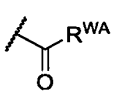
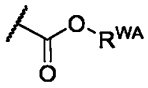
[0046] 或其药学上可接受的盐,其中:

[0047] R^5是-R^{5A}-L^5-R^{5B};

[0048] R^{5A}是R^B之二价基团,其中除-L^5-R^{5B}之外,R^{5A}还经m个R^{5C}实例取代;

[0049] R^{5B}是氢或R^B,其中R^{5B}经n个R^{5D}实例取代;

[0050] Cy^6是亚苯基或具有1至3个氮原子的6元亚杂芳基,其中除-L^6-R^W之外,Cy^6还经p个R^6实例取代;

[0051] R^W是卤素、-CN、  、  、  、  、  、  、  、  、  、  或  ；

[0052] R^6的各实例独立地是R^A或R^B，其中R^6经q个R^C实例取代；或

[0053] 两个R^6实例，或一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环；其中所述环经$_r$个R^C实例取代；

[0054] R^7是H或R^B，其中R^7经t个R^{7A}实例取代；

[0055] L^5及L^6中的每一者独立地是共价键，或C_{1-4}饱和或不饱和、直链或分支链二价烃链，其中所述链的一或两个亚甲基单元任选地且独立地经以下置换：-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-；

[0056] R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR，或选自以下的任选地经取代的基团：C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环，及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环；或

[0057] R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例，或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环；

[0058] R^{WD}是卤素或-OS(O)$_2$R；

[0059] R^{5C}、R^{5D}、R^{7A}及R^L的各实例独立地是R^A或R^B，且经u个R^C实例取代；

[0060] R^A的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$或-N(R)S(O)$_2$R；

[0061] R^B的各实例独立地是C_{1-6}脂肪族；苯基；具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环；具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环；3至7元饱和或部分不饱和碳环；具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环；或具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环；

[0062] R^C的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-S(O)$_2$F、-OS(O)$_2$F、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R，或选自以下的任选地经取代的基团：$C_{1-6}$脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环，及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环；

[0063] 各R独立地是氢或选自以下的任选地经取代的基团:C_{1-6}脂肪族;苯基;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环;及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环,或:

[0064] 同一氮上的两个R基团与其间插原子一起形成4至7元饱和、部分不饱和或杂芳基环,除所述氮之外,所述杂芳基环还具有0至3个独立地选自氮、氧及硫的杂原子;

[0065] m、n、p、q、r、t及u中的每一者独立地是0、1、2、3或4。

[0066] 2.化合物及定义

[0067] 本发明化合物包括本文中一般描述的那些物,且根据本文所公开的类别、子类及种类进一步说明。如本文所用,除非另有指示,否则以下定义应适用。出于本发明的目的,化学元素是根据元素周期表CAS版(《化学和物理手册(Handbook of Chemistry and Physics)》第75版)来鉴别。此外,有机化学的一般原理描述于"有机化学(Organic Chemistry)",托马斯·索瑞尔(Thomas Sorrell),大学科学出版社(University Science Books),索萨力拓(Sausalito):1999及"马奇高级有机化学(March′s Advanced Organic Chemistry)"第5版,编者:史密斯M.B.(Smith,M.B.)及马奇J.(March,J.),约翰·威利父子公司(John Wiley&Sons),纽约(New York):2001,所述文献的全部内容以引用的方式并入本文中。化学名称、通用名称及化学结构可互换使用以描述相同结构。若使用化学结构与化学名称提及化合物且结构与名称存在分歧,则以结构为准。

[0068] 如本文所用,术语"脂肪族"或"脂肪族基团"意指经取代或未经取代的完全饱和或含有一或多个不饱和单元的直链(即,非分支链)或分支链烃链,或完全饱和或含有一或多个不饱和单元、但不是芳香族(在本文中也称为"碳环"或"环脂肪族")的单环烃或双环烃,其具有连至分子的其余部分的单个连接点。除非另外指定,否则脂肪族基团含有1至6个脂肪族碳原子。在一些实施例中,脂肪族基含有1至5个脂肪族碳原子。在其它实施例中,脂肪族基含有1至4个脂肪族碳原子。在另外的其它实施例中,脂肪族基含有1至3个脂肪族碳原子,且在又其它实施例中,脂肪族基含有1至2个脂肪族碳原子。在一些实施例中,"环脂肪族"(或"碳环")是指完全饱和或含有一或多个不饱和单元,但不是芳香族的单环C_3-C_6烃,其具有连至分子的其余部分的单个连接点。适合的脂肪族基包括(但不限于)直链或分支链、经取代或未经取代的烷基、烯基、炔基及其混合物,例如(环烷基)烷基、(环烯基)烷基或(环烷基)烯基。

[0069] 除非另外指明,否则如本文所用,术语"烷基"是指具有直链、分支链、单环部分或多环部分或其组合的单价脂肪族烃基,其中所述基团任选地在直链、分支链、单环部分或多环部分或其组合的一或多个碳原子处经各碳处的一或多个取代基取代,其中所述一或多个取代基独立地是C_1-C_{10}烷基。"烷基"的实例包括甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基、叔丁基、戊基、己基、庚基、环丙基、环丁基、环戊基、环己基、环庚基、降冰片烷基及其类似基团。

[0070] 术语"低碳数烷基"是指C_{1-4}直链或分支链烷基。示例性低碳数烷基是甲基、乙基、丙基、异丙基、丁基、异丁基及叔丁基。

[0071] 术语"低碳数卤烷基"是指经一或多个卤素原子取代的C_{1-4}直链或分支链烷基。

[0072] 术语"杂原子"意指氧、硫、氮、磷或硅中的一或多者(包括氮、硫、磷或硅的任何氧化形式;任何碱氮的季铵化形式;或杂环的可取代氮,例如N(如3,4-二氢-2H-吡咯基中)、NH

(如吡咯烷基中)或NR^+(如N上经取代的吡咯烷基中))。

[0073] 如本文所用,术语“不饱和”意指部分具有一或多个不饱和单元。

[0074] 如本文所用,术语“C_{1-8}(或C_{1-6}或C_{1-4})饱和或不饱和、直链或分支链二价烃链”是指如本文所定义为直链或分支链的二价亚烷基、亚烯基及亚炔基链。

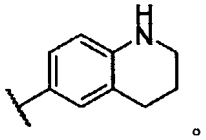
[0075] 术语“亚烷基”是指二价烷基。“亚烷基链”为聚亚甲基,即-$(CH_2)_n$-,其中n是正整数,优选1至6、1至4、1至3、1至2或2至3。经取代的亚烷基链是其中一或多个亚甲基氢原子由取代基置换的聚亚甲基。适合取代基包括下文关于经取代的脂肪族基所述的那些取代基。

[0076] 术语“亚烯基”是指二价烯基。经取代的亚烯基链为含有至少一个双键的聚亚甲基,其中一或多个氢原子经取代基置换。适合取代基包括下文关于经取代的脂肪族基所述的那些取代基。

[0077] 术语“卤素”“意指F、Cl、Br或I。

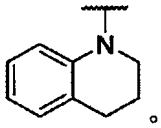
[0078] 单独使用或作为较大部分(如“芳烷基”、“芳烷氧基”或“芳氧基烷基”)的一部分使用的术语“芳基”是指具有总共五至十四个环成员的单环或双环系统,其中系统中的至少一个环为芳香族且其中系统中的各环含有3至7个环成员。术语“芳基”可与术语“芳环”互换使用。在本发明的某些实施例中,“芳基”是指可具有一或多个取代基的芳环系统,包括(但不限于)苯基、联苯、萘基、蒽基及其类似基团。

[0079] 除非另外定义,否则如本文所用,术语“杂芳基”或“杂芳香族”是指含有一或多个杂原子(例如一至三个杂原子,例如氮、氧及硫)的5至6元单环芳香族环,或含有一或多个杂原子的8至10元多环环系统,其中多环环系统中的至少一个环为芳香族,且多环环系统的连接点是经由芳香族环上的环原子。杂芳基环可以经由碳或氮连接至相邻基团。杂芳基环的实例包括(但不限于)呋喃、噻吩、吡咯、噻唑、恶唑、异噻唑、异恶唑、咪唑、吡唑、三唑、吡啶、嘧啶、吲哚等。举例来说,除非另外定义,否则1,2,3,4-四氢喹啉为杂芳基环,条件是其连接点经由苯并环,例如:

[0080]  。

[0081] 除非另外定义,否则术语“杂环基”或“杂环基团”是指饱和或部分不饱和的3至10元单环或7至14元多环环系统,包括桥连或稠合环,且其环系统包括一至四个杂原子,例如氮、氧及硫。杂环基环可经由碳或氮连接至相邻基团。

[0082] 除非另外定义,否则术语“部分不饱和”在环的上下文中是指单环,或多环(例如双环、三环等)环系统内的组成环,其中所述组成环含有至少一个除环自身所提供的不饱和度之外的不饱和度,但不为芳香族。部分不饱和环的实例包括(但不限于)3,4-二氢-2H-哌喃、3-吡咯啉、2-噻唑啉等。在部分不饱和环为多环环系统的一部分的情况下,多环环系统中的其它组成环可为饱和、部分不饱和的或芳香族,但多环环系统的连接点位于部分不饱和组成环上。举例来说,除非另外定义,否则1,2,3,4-四氢喹啉为部分不饱和环,条件是其连接点系经由哌啶基环,例如:

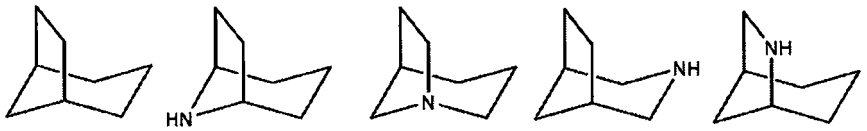
[0083]  。

[0084] 除非另外定义,否则术语“饱和”在环的上下文中是指3至10元单环或7至14元多环(例如双环、三环等)环系统,其中所述单环或作为多环环系统的连接点的组成环不含除环自身所提供的不饱和度之外的额外不饱和度。单环饱和环的实例包括(但不限于)氮杂环丁烷、氧杂环丁烷、环已烷等。在饱和环为多环环系统的一部分的情况下,多环环系统中的其它组成环可为饱和、部分不饱和的或芳香族,但多环环系统的连接点位于饱和组成环上。举例来说,除非另外定义,否则2-氮杂螺[3.4]辛-6-烯为饱和环,条件是其连接点系经由N-氮杂环丁烷基环,例如:

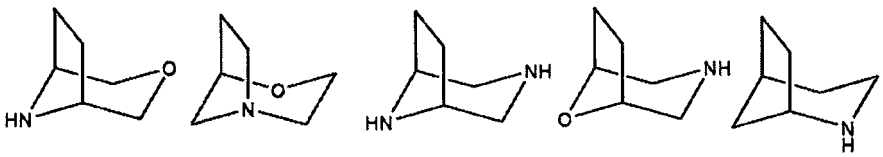
[0085] 。

[0086] 如本文所用,术语“亚烷基”、“亚芳基”、“亚环烷基”、“亚杂芳基”、“亚杂环烷基”及具有前缀“亚-”的其它类似术语是指由所述前缀修饰的基团的二价键结形式。举例来说,“亚烷基”为二价烷基,其使基团连接至其所连接者。

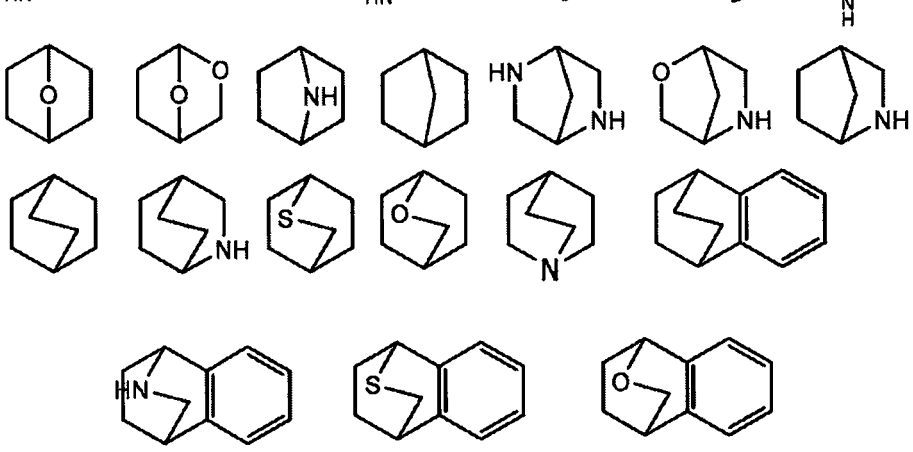
[0087] 如本文所用,术语“桥连双环”是指具有至少一个桥键的任何饱和或部分不饱和双环系统,即,碳环或杂环。如IUPAC所定义,“桥键”为多个原子或一个原子的未分支链或连接两个桥头的价键,其中“桥头”是与三个或更多个骨架原子(除氢以外)键结的环系统的任何骨架原子。在一些实施例中,桥连双环基团具有7至12个环成员及0至4个独立地选自氮、氧或硫的杂原子。此类桥连双环基团为本领域中所熟知,且包括在下文中阐述之那些基团,其中各基团在任何可取代碳或氮原子处与分子的其余部分连接。除非另外说明,否则桥连双环基团任选地经一或多个如关于脂肪族基阐述之取代基取代。或者或另外,桥连双环基团之任何可取代氮任选地经取代。示例性桥连双环包括:



[0088]



[0089]

 。

[0090] 如本文所述,本发明化合物可含有“任选地经取代”的部分。一般而言,术语“经取代”无论前面是否有术语“任选地”均意指指定部分之一或多个氢经适合的取代基置换。除非另有指示,否则“任选地经取代”的基团可在基团之各可取代位置处具有适合的取代基,

且当任何指定结构中的超过一个位置可经超过一个选自指定基团之取代基取代时,在每一位置处之取代基可相同或不同。本发明所设想之取代基之组合优选引起稳定或化学上可行的化合物形成的那些取代基组合。如本文所用,术语“稳定”是指化合物在经受允许其产生、侦测及(在某些实施例中)其回收、纯化及用于本文所公开的一或多种目的之条件时不发生实质上改变。

[0091] “任选地经取代”的基团之可取代碳原子上的适合单价取代基独立地是卤素;-$(CH_2)_{0-4}R^{\bigcirc}$;-$(CH_2)_{0-4}OR^{\bigcirc}$;-O$(CH_2)_{0-4}R^{\bigcirc}$;-O-$(CH_2)_{0-4}C(O)OR^{\bigcirc}$;-$(CH_2)_{0-4}CH(OR^{\bigcirc})_2$;-$(CH_2)_{0-4}SR^{\bigcirc}$;可经$R^{\bigcirc}$取代的-$(CH_2)_{0-4}Ph$;可经$R^{\bigcirc}$取代的-$(CH_2)_{0-4}O(CH_2)_{0-1}Ph$;可经$R^{\bigcirc}$取代的-CH=CHPh;可经$R^{\bigcirc}$取代的-$(CH_2)_{0-4}O(CH_2)_{0-1}$-吡啶基;-$NO_2$;-CN;-$N_3$;-$(CH_2)_{0-4}N(R^{\bigcirc})_2$;-$(CH_2)_{0-4}N(R^{\bigcirc})C(O)R^{\bigcirc}$;-$N(R^{\bigcirc})C(S)R^{\bigcirc}$;-$(CH_2)_{0-4}N(R^{\bigcirc})C(O)NR^{\bigcirc}_2$;-$N(R^{\bigcirc})C(S)NR^{\bigcirc}_2$;-$(CH_2)_{0-4}N(R^{\bigcirc})C(O)OR^{\bigcirc}$;-$N(R^{\bigcirc})N(R^{\bigcirc})C(O)R^{\bigcirc}$;-$N(R^{\bigcirc})N(R^{\bigcirc})C(O)NR^{\bigcirc}_2$;-$N(R^{\bigcirc})N(R^{\bigcirc})C(O)OR^{\bigcirc}$;-$(CH_2)_{0-4}C(O)R^{\bigcirc}$;-$C(S)R^{\bigcirc}$;-$(CH_2)_{0-4}C(O)OR^{\bigcirc}$;-$(CH_2)_{0-4}C(O)SR^{\bigcirc}$;-$(CH_2)_{0-4}C(O)OSiR^{\bigcirc}_3$;-$(CH_2)_{0-4}OC(O)R^{\bigcirc}$;-OC(O)$(CH_2)_{0-4}SR^{\bigcirc}$;-SC(S)$SR^{\bigcirc}$;-$(CH_2)_{0-4}SC(O)R^{\bigcirc}$;-$(CH_2)_{0-4}C(O)NR^{\bigcirc}_2$;-$C(S)NR^{\bigcirc}_2$;-$C(S)SR^{\bigcirc}$;-SC(S)$SR^{\bigcirc}$;-$(CH_2)_{0-4}OC(O)NR^{\bigcirc}_2$;-C(O)N$(OR^{\bigcirc})R^{\bigcirc}$;-C(O)C(O)$R^{\bigcirc}$;-C(O)$CH_2C(O)R^{\bigcirc}$;-C$(NOR^{\bigcirc})R^{\bigcirc}$;-$(CH_2)_{0-4}SSR^{\bigcirc}$;-$(CH_2)_{0-4}S(O)_2R^{\bigcirc}$;-$(CH_2)_{0-4}S(O)_2OR^{\bigcirc}$;-$(CH_2)_{0-4}OS(O)_2R^{\bigcirc}$;-$S(O)_2NR^{\bigcirc}_2$;-$(CH_2)_{0-4}S(O)R^{\bigcirc}$;-$N(R^{\bigcirc})S(O)_2NR^{\bigcirc}_2$;-$N(R^{\bigcirc})S(O)_2R^{\bigcirc}$;-$N(OR^{\bigcirc})R^{\bigcirc}$;-$C(NH)NR^{\bigcirc}_2$;-P(O)$(OR^{\bigcirc})R^{\bigcirc}$;-$P(O)R^{\bigcirc}_2$;-OP(O)$R^{\bigcirc}_2$;-OP(O)$(OR^{\bigcirc})_2$;-$SiR^{\bigcirc}_3$;-($C_{1-4}$直链或分支链亚烷基)O-$N(R^{\bigcirc})_2$;或-($C_{1-4}$直链或分支链亚烷基)C(O)O-$N(R^{\bigcirc})_2$,其中各$R^{\bigcirc}$可如下文所定义经取代且独立地是氢、$C_{1-6}$脂肪族、-$CH_2Ph$、-O$(CH_2)_{0-1}Ph$、-$CH_2$-(5至6元杂芳基环),或具有0至4个独立地选自氮、氧或硫的杂原子的5至6元饱和、部分不饱和或芳环,或不管上述定义,两个独立出现的$R^{\bigcirc}$与其间插原子一起形成具有0至4个独立地选自氮、氧或硫的杂原子的3至12元饱和、部分不饱和或芳基单环或双环,所述环可以如下文所定义经取代。

[0092] $R^{\bigcirc}$上之适合单价取代基(或两个单独出现之$R^{\bigcirc}$与其间插原子一起形成之环)独立地是卤素、-$(CH_2)_{0-2}R^{\bullet}$、-(卤基$R^{\bullet}$)、-$(CH_2)_{0-2}OH$、-$(CH_2)_{0-2}OR^{\bullet}$、-$(CH_2)_{0-2}CH(OR^{\bullet})_2$;-O(卤基$R^{\bullet}$)、-CN、-$N_3$、-$(CH_2)_{0-2}C(O)R^{\bullet}$、-$(CH_2)_{0-2}C(O)OH$、-$(CH_2)_{0-2}C(O)OR^{\bullet}$、-$(CH_2)_{0-2}SR^{\bullet}$、-$(CH_2)_{0-2}SH$、-$(CH_2)_{0-2}NH_2$、-$(CH_2)_{0-2}NHR^{\bullet}$、-$(CH_2)_{0-2}NR^{\bullet}_2$、-$NO_2$、-$SiR^{\bullet}_3$、-$OSiR^{\bullet}_3$、-$C(O)SR^{\bullet}$、-($C_{1-4}$直链或分支链亚烷基)$C(O)OR^{\bullet}$或-$SSR^{\bullet}$,其中各$R^{\bullet}$未经取代或在冠有“卤基”的情况下仅经一或多种卤素取代,且独立地选自C_{1-4}脂肪族、-CH_2Ph、-O$(CH_2)_{0-1}Ph$或具有0至4个独立地选自氮、氧或硫的杂原子的5至6元饱和、部分不饱和或芳环。$R^{\bigcirc}$之饱和碳原子上的适合二价取代基包括=O及=S。

[0093] “任选地经取代”的基团之饱和碳原子上的适合二价取代基包括以下:=O、=S、=NNR^*_2、=NNHC(O)R^*、=NNHC(O)OR^*、=NNHS$(O)_2R^*$、=NR^*、=NOR^*、-O$(C(R^*_2))_{2-3}$O-或-S$(C(R^*_2))_{2-3}$S-,其中各单独出现之R^*是选自氢、可如下文所定义经取代的C_{1-6}脂肪族,或具有0至4个独立地选自氮、氧或硫的杂原子的未经取代的5至6元饱和、部分不饱和或芳环。结合至“任选地经取代的”基团之邻位可取代碳的适合二价取代基包括:-O$(CR^*_2)_{2-3}$O-,其中各单独出现之R^*是选自氢、可如下文所定义经取代的C_{1-6}脂肪族基,或具有0至4个独立地选自氮、氧或硫的杂原子的未经取代的5至6元饱和、部分不饱和或芳环。

[0094] R^*之脂肪族基团上的适合取代基包括卤素、-$R^{\bullet}$、-(卤基$R^{\bullet}$)、-OH、-$OR^{\bullet}$、-O(卤基$R^{\bullet}$)、-CN、-C(O)OH、-C(O)$OR^{\bullet}$、-NH_2、-$NHR^{\bullet}$、-$NR^{\bullet}_2$或-NO_2,其中各$R^{\bullet}$未经取代或在冠有“卤基”

的情况下仅经一或多个卤素取代且独立地是C_{1-4}脂肪族、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$，或具有0至4个独立地选自氮、氧或硫的杂原子的5至6元饱和、部分不饱和或芳环。

[0095] “任选地经取代的”基团之可取代氮上的适合取代基包括$-R^{\dagger}$、$-NR^{\dagger}_2$、$-C(O)R^{\dagger}$、$-C(O)OR^{\dagger}$、$-C(O)O(O)R^{\dagger}$、$-C(O)CH_2C(O)R^{\dagger}$、$-S(O)_2R^{\dagger}$、$-S(O)_2NR^{\dagger}_2$、$-C(S)NR^{\dagger}_2$、$-C(NH)NR^{\dagger}_2$或$-N(R^{\dagger})S(O)_2R^{\dagger}$；其中各$R^{\dagger}$独立地是氢、可如下文所定义经取代的$C_{1-6}$脂肪族、未经取代的-OPh或具有0至4个独立地选自氮、氧或硫的杂原子的未经取代的5至6元饱和、部分不饱和或芳环；或不管上述定义，两个单独出现之$R^{\dagger}$与其间插原子一起形成具有0至4个独立地选自氮、氧或硫的杂原子的未经取代的3至12元饱和、部分不饱和或芳基单环或双环。

[0096] $R^{\dagger}$之脂肪族基团上的适合取代基独立地是卤素、$-R^{\bullet}$、-(卤基$R^{\bullet}$)、-OH、$-OR^{\bullet}$、-O(卤基$R^{\bullet}$)、-CN、-C(O)OH、$-C(O)OR^{\bullet}$、$-NH_2$、$-NHR^{\bullet}$、$-NR^{\bullet}_2$或$-NO_2$，其中各$R^{\bullet}$未经取代或在冠有“卤基”的情况下仅经一或多个卤素取代，且独立地是C_{1-4}脂肪族、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$，具有0至4个独立地选自氮、氧或硫的杂原子的5至6元饱和、部分不饱和或芳环。

[0097] 如本文所用，术语“异构体”是指具有相同化学式、但结构或光学组态不同的化合物。如本文所用，术语“立体异构体”是指且包括具有相同分子式、但原子和/或官能基在空间中定位不同的异构分子。本发明化合物的所有立体异构体(例如，由于各个取代基上之不对称碳而可能存在的那些立体异构体)，包括对映异构形式及非对映异构形式，涵盖在本公开的范畴内。因此，除非另有说明，否则本发明化合物的单一立体化学异构体以及对映异构体、非对映异构体及几何(或构象)异构体的混合物处于本发明的范畴内。

[0098] 如本文所用，术语“互变异构体”为平衡存在且容易自一种异构形式转化成另一种异构形式的两种或更多种结构异构体之一。应理解，互变异构体涵盖价态互变异构体及质子互变异构体(也称为质子移变的互变异构体)。价态互变异构体包括一些键结电子重组所引起的相互转化。质子互变异构体包括经由质子迁移发生的相互转化，例如酮-烯醇及亚胺-烯胺异构化。除非另外说明，否则本发明化合物的所有互变异构体均在本发明的范畴内。

[0099] 如本文所用，术语“同位素取代”是指原子经其同位素取代。如本文所用，术语“同位素”是指与自然界中主要存在的原子具有相同原子数、但质量数(中子数)与自然界中主要存在的原子之质量数不同的原子。应理解，具有同位素取代的化合物是指其中所含有的至少一个原子经其同位素取代的化合物。可经其同位素取代的原子包括(但不限于)氢、碳及氧。氢原子同位素的实例包括^{2}H(亦表示为D)及^{3}H。碳原子同位素的实例包括^{13}C及^{14}C。氧原子同位素的实例包括^{18}O。除非另外说明，否则本发明化合物的所有同位素取代均在本发明的范畴内。此类化合物适用作例如分析工具，用作生物分析中的探针，或用作根据本发明的治疗剂。在某些实施例中，举例来说，所提供的化合物的弹头部分R^{W}包含一或多个氘原子。

[0100] 如本文所用，术语“药学上可接受的盐”是指在合理医学判断的范围内，适于与人类及低等动物的组织接触使用而无过度毒性、刺激、过敏反应及类似情形且与合理的效益/风险比相称的那些盐。示例性药学上可接受的盐见于例如Berge等人(J.Pharm.Sci.1977,66(1),1;及Gould,P.L.,Int.J.Pharmaceutics 1986,33,201-217中;(每一者以全文引用的方式并入本文)。

[0101] 本发明化合物的药学上可接受的盐包括衍生自适合无机及有机酸及碱之那些盐。药学上可接受的无毒性酸加成盐的实例为氨基与无机酸(例如盐酸、氢溴酸、磷酸、硫酸及过氯酸)或与有机酸(例如乙酸、草酸、顺丁烯二酸、酒石酸、柠檬酸、丁二酸或丙二酸)形成之盐,或通过使用本领域中所使用之其它方法(例如离子交换)形成之盐。其它药学上可接受的盐包括己二酸盐、褐藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷丙酸盐、二葡糖酸盐、十二烷基硫酸盐、乙烷磺酸盐、甲酸盐、反丁烯二酸盐、葡庚糖酸盐、甘油磷酸盐、葡糖酸盐、半硫酸盐、庚酸盐、已酸盐、氢碘化物、2-羟基-乙烷磺酸盐、乳糖酸盐、乳酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、顺丁烯二酸盐、丙二酸盐、甲烷磺酸盐、2-萘磺酸盐、烟碱酸盐、硝酸盐、油酸盐、草酸盐、棕榈酸盐、双羟萘酸盐、果胶酸盐、过硫酸盐、3-苯基丙酸盐、磷酸盐、特戊酸盐、丙酸盐、硬脂酸盐、丁二酸盐、硫酸盐、酒石酸盐、硫氰酸盐、对甲苯磺酸盐、十一烷酸盐、戊酸盐及其类似盐。

[0102] 衍生自适当碱的盐包括碱金属、碱土金属、铵及$N^+(C_{1-4}烷基)_4$盐。代表性碱金属或碱土金属盐包括钠盐、锂盐、钾盐、钙盐、镁盐及其类似盐。适当时,药学上可接受的其它盐包括无毒铵、季铵及使用例如卤离子、氢氧根、羧酸根、硫酸根、磷酸根、硝酸根、低碳烷基磺酸根及芳基磺酸根之相对离子形成之胺阳离子。

[0103] 药学上可接受的盐亦意欲涵盖半盐,其中化合物:酸之比率分别为2:1。示例性半盐为衍生自包含两个羧酸基之酸的那些盐,所述酸例如苹果酸、反丁烯二酸、顺丁烯二酸、丁二酸、酒石酸、戊二酸、草酸、己二酸及柠檬酸。其它示例性半盐为衍生自二质子矿物酸(例如硫酸)之那些盐。优选示例性半盐包括(但不限于)半顺丁烯二酸盐、半反丁烯二酸盐及半丁二酸盐。

[0104] 如本文所用,术语“约”在本文中用于指大约、大致、在...左右或在...附近。当术语“约”结合数值范围使用时,其通过扩展界限高于及低于所述数值来修饰所述范围。一般而言,术语“约”在本文中用于修饰数值高于及低于所述值:向上或向下(更高或更低)20%的偏差。

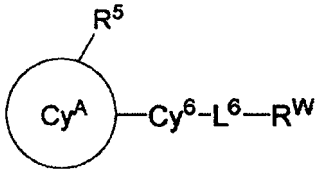
[0105] 如本文所用,“有效量”、“足量”或“治疗有效量”系足以实现有益或所要结果(包括临床结果)的化合物的量。因此,有效量可足以例如减轻或改善与FGFR2信号传导有关的疾患之严重程度和/或持续时间或其一或多种症状;预防与FGFR2信号传导有关的疾患相关病状或症状的进展;或者增强或以其它方式改善另一疗法之预防或治疗效果。有效量亦包括避免或实质上减弱非所要副作用的化合物的量。

[0106] 如本文所用且如本领域中所充分了解,“治疗”为获得有益或所需结果(包括临床结果)之途径。有益或所需临床结果可以包括(但不限于)一或多种症状或病状的缓解或改善、疾病或病痛之程度减轻、疾病或病痛之状态稳定(即不恶化)、疾病或病痛扩散之预防、疾病或病痛进展之延迟或减缓、疾病或病痛状态之改善或缓和,以及缓解(无论部分或全部),无论可侦测或不可侦测。“治疗”也可意指存活期与未接受治疗之预期存活期相比延长。在一些实施例中,可在一或多种症状已出现之后施用疗法。在其它实施例中,疗法可在不存在症状的情况下施用。举例来说,疗法可在症状发作之前施用于易感个体(例如,根据症状病史和/或根据遗传或其它易感因素)。也可在症状已消退之后继续治疗,例如预防或延迟其复发。

[0107] 词组“有需要”是指需要从与FGFR2信号传导活性有关的病状中出现有症状的或无症状的缓解,或可以其它方式通过本公开的化合物和/或组合物缓解。

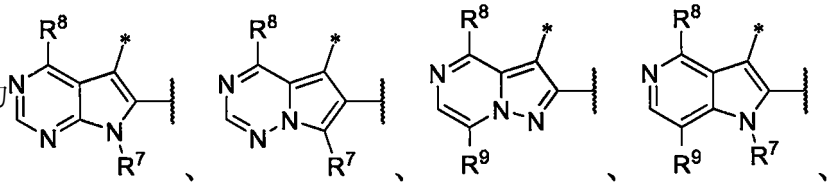
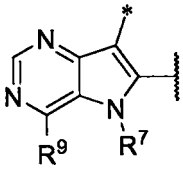
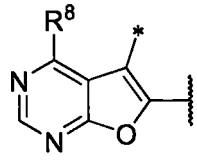
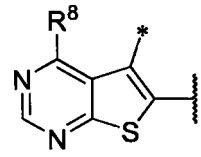
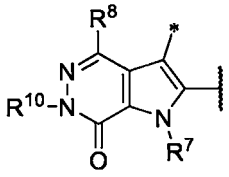
[0108] 3.示例性实施例之描述

[0109] 如上文所述,在一些实施例中,本发明提供式I-1化合物:

[0110] 

I-1

[0111] 或其药学上可接受的盐,其中:

[0112] Cy^A为  、、、、  、  、  或  ,

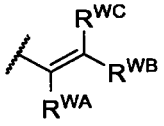
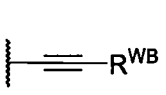
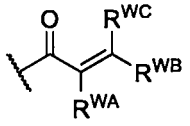
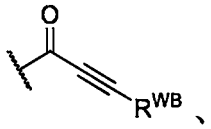
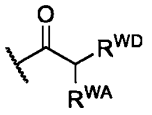
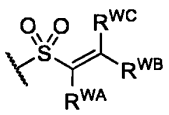
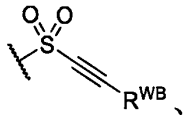
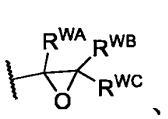
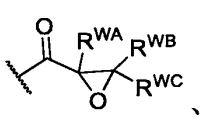
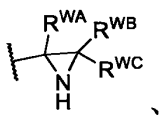
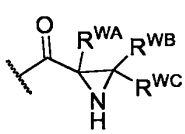
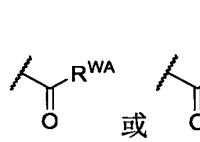
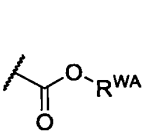
[0113] 其中↗表示连至R^5之键结且↘表示连至Cy^6之键结;

[0114] R^5为-R^{5A}-L^5-R^{5B};

[0115] R^{5A}为R^B之二价基团,其中除-L^5-R^{5B}之外,R^{5A}还经m个R^{5C}实例取代;

[0116] R^{5B}为氢或R^B,其中R^{5B}经n个R^{5D}实例取代;

[0117] Cy^6为亚苯基;3至14元饱和或部分不饱和二价碳环;具有1至4个独立地选自氮、氧及硫的杂原子的3至14元饱和或部分不饱和二价杂环;或具有1至4个独立地选自氮、氧及硫的杂原子的5至14元亚杂芳基;其中除-L^6-R^W之外,Cy^6还经p个R^6实例取代;

[0118] R^W是卤素、-CN、  、  、  、  、  、  、  、  、  、  、  、  或  ;

[0119] R^6的各实例独立地是R^A或R^B,其中R^6经q个R^C实例取代:或

[0120] 两个R^6实例、一个R^6实例及一个R^L实例、一个R^6实例及一个R^{WA}实例,或一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至8元部分不饱和或芳香族环,其中所述环经r个R^C实例取代;

[0121] R^7是H或R^B,其中R^7经t个R^{7A}实例取代;

[0122] R^8是H、-NR_2、卤素、-OH,或任选地经1至3个卤素取代的C_{1-6}脂肪族;

[0123] R^9是H、-NR_2、卤素,或任选地经1至3个卤素取代的C_{1-6}脂肪族;

[0124] R^{10}是H或任选地经1至3个卤素取代的C_{1-6}脂肪族;

[0125] L^5及L^6中的每一者独立地是共价键,或C_{1-4}饱和或不饱和、直链或分支链二价烃链,其中所述链中的一或两个亚甲基单元任选地且独立地经以下置换:-$CH(R^L)$-、-$C(R^L)_2$-、C_{3-6}亚环烷基、3至6元亚杂环烷基、5至6元亚杂芳基、-NH-、-$N(R^L)$-、-NHC(O)-、-$N(R^L)$C(O)-、-C(O)NH-、-C(O)$N(R^L)$-、-$NHS(O)_2$-、-$N(R^L)S(O)_2$-、-$S(O)_2NH$-、-$S(O)_2N(R^L)$-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-$S(O)_2$-;其中所述C_{3-6}亚环烷基、3至6元亚杂环烷基及5至6元亚杂芳基中的每一者任选地经一个R^A或C_{1-6}脂肪族实例取代;

[0126] R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;或

[0127] R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例,或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环;其中所述环经w个R^C实例取代;

[0128] R^{WD}是卤素或-$OS(O)_2R$;

[0129] R^{5C}、R^{5D}、R^{7A}及R^L的各实例独立地是R^A或R^B,且经u个R^C实例取代;或

[0130] 两个R^{5C}实例、一个R^{5C}实例及一个R^{5D}实例,或两个R^{5D}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的3至7元饱和、部分不饱和或芳香族环;其中所述环经v个R^C实例取代;

[0131] R^A的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-$S(O)_2R$、-$S(O)_2NR_2$、-S(O)R、-$S(O)NR_2$、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-$N(R)S(O)_2NR_2$或-$N(R)S(O)_2R$;

[0132] R^B的各实例独立地是C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;或具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环;

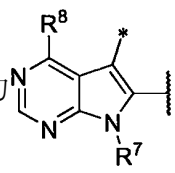
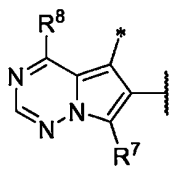
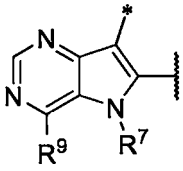
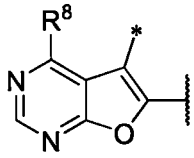
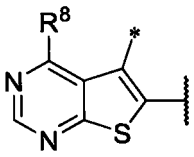
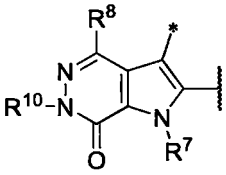
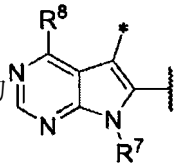
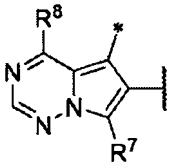
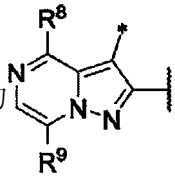
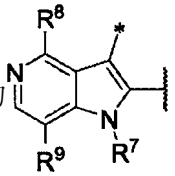
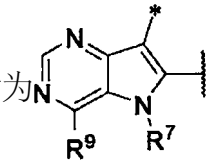
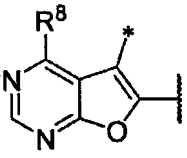
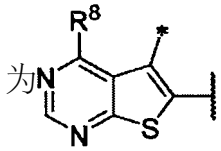
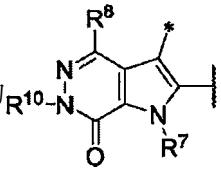
[0133] R^C的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-$S(O)_2R$、-$S(O)_2NR_2$、-S(O)R、-$S(O)NR_2$、-$S(O)_2F$、-$OS(O)_2F$、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-$N(R)S(O)_2NR_2$、-$N(R)S(O)_2R$,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;

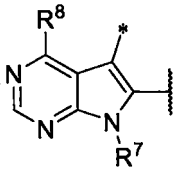
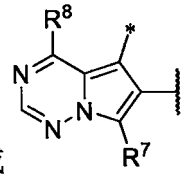
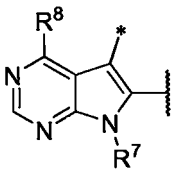
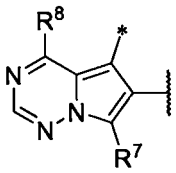
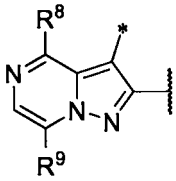
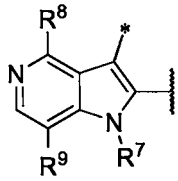
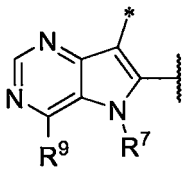
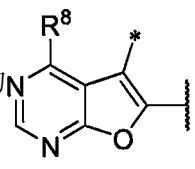
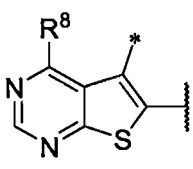
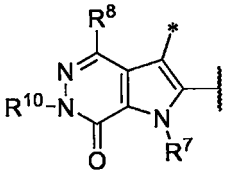
[0134] 各R独立地是氢或选自以下的任选地经取代的基团:C_{1-6}脂肪族;苯基;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环;及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环,或:

[0135] 同一氮上的两个R基团与其间插原子一起形成4至7元饱和、部分不饱和或杂芳基

环,除所述氮之外,所述环还具有0至3个独立地选自氮、氧及硫的杂原子;

[0136] m、n、p、q、r、t、u、v及w中的每一者独立地是0、1、2、3或4。

[0137] 如上文一般性定义,Cy^A为  、  、 、 、  、  、  或  ,其中*表示连至R^5之键结且*表示连至Cy^6之键结。在一些实施例中,Cy^A为  。在一些实施例中,Cy^A为  。在一些实施例中,Cy^A为  。在一些实施例中,Cy^A为  。在一些实施例中,Cy^A为  。在一些实施例中,Cy^A为  。在一些实施例中,Cy^A为  。在一些实施例中,Cy^A为  。

[0138] 在一些实施例中,Cy^A为  或  。在一些实施例中,Cy^A为  、  、  、  或  。在一些实施例中,Cy^A为  、  或  。在一些实施例中,Cy^A是选自表1的化合物中所描绘的基团。

[0139] 如上文一般所定义，Cy^6为亚苯基；饱和或部分不饱和3至14元二价碳环；具有1至4个独立地选自氮、氧及硫的杂原子的饱和或部分不饱和二价3至14元杂环；或具有1至4个独立地选自氮、氧及硫的杂原子的5至14元亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

[0140] 在一些实施例中，Cy^6为亚苯基；3至7元饱和或部分不饱和二价单环碳环；8至14元饱和或部分不饱和二价双环碳环；具有1至4个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和二价单环杂环；或具有1至4个独立地选自氮、氧及硫的杂原子的8至14元饱和或部分不饱和二价双环杂环；具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环亚杂芳基；或具有1至4个独立地选自氮、氧及硫的杂原子的9至10元双环亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

[0141] 在一些实施例中，Cy^6为3至14元饱和或部分不饱和二价碳环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6为3至7元饱和或部分不饱和二价单环碳环，或8至14元饱和或部分不饱和二价双环碳环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6为3至7元饱和或部分不饱和二价单环碳环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6为8至14元饱和或部分不饱和二价双环碳环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

[0142] 在一些实施例中，Cy^6是具有1至4个独立地选自氮、氧及硫的杂原子的3至14元饱和或部分不饱和二价杂环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6是具有1至4个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和二价单环杂环；或具有1至4个独立地选自氮、氧及硫的杂原子的8至14元饱和或部分不饱和二价双环杂环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

[0143] 在一些实施例中，Cy^6是具有1至4个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和二价单环杂环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6是具有1至2个独立地选自氮、氧及硫的杂原子的5至6元饱和或部分不饱和二价单环杂环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6为二价吡咯烷或二氢吡咯烷环；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

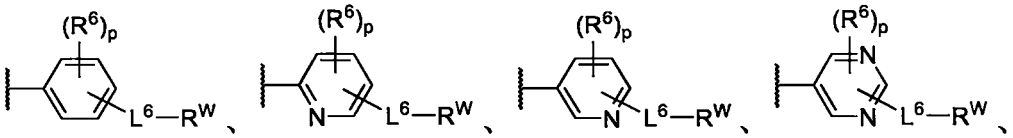
[0144] 在一些实施例中，Cy^6是具有1至4个独立地选自氮、氧及硫的杂原子的5至14元亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6是具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环亚杂芳基；或具有1至4个独立地选自氮、氧及硫的杂原子的9至10元双环亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

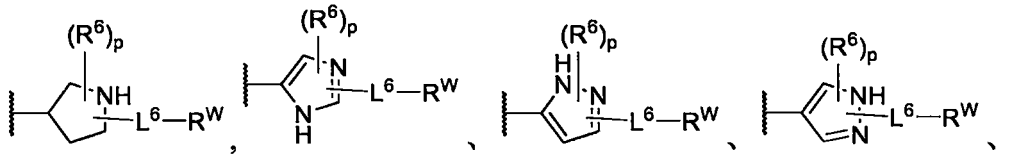
[0145] 在一些实施例中，Cy^6是具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6是具有1至2个氮原子的5至6元单环亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6是具有1至2个氮原子的5元单环亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

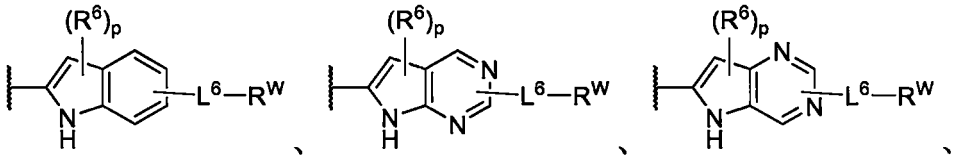
[0146] 在一些实施例中，Cy^6为1至4个独立地选自氮、氧及硫的杂原子的9至10元双环亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。在一些实施例中，Cy^6是具有1至3个氮原子的9至10元双环亚杂芳基；其中除$-L^6-R^W$之外，Cy^6还经p个R^6实例取代。

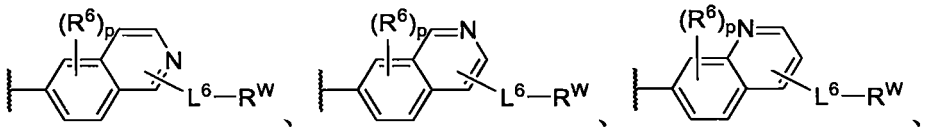
[0147] 在一些实施例中，Cy^6是选自表1的化合物中所描绘的基团。

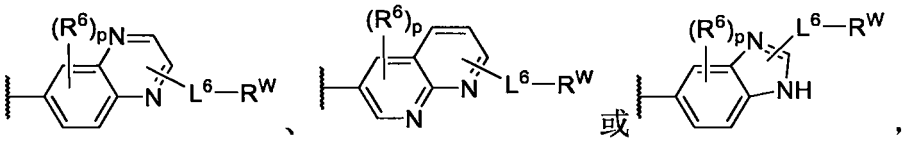
[0148] 在一些实施例中，$-Cy^6-L^6-R^W$结合在一起是：



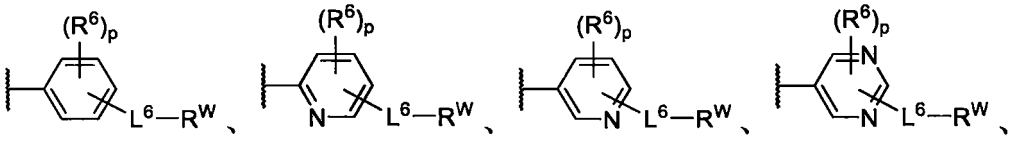


[0149] 

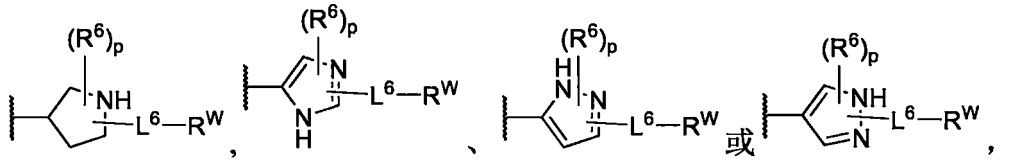




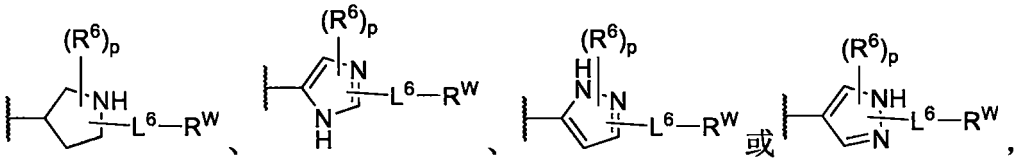
[0150] 其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:



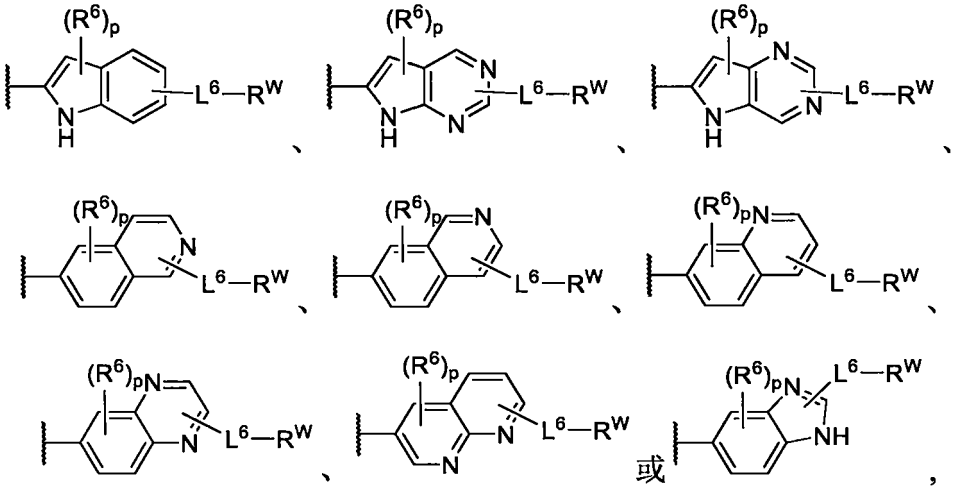
[0151]



[0152] 其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:

[0153] 

[0154] 其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:

[0155] 

[0156] 其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。

[0157] 如上文一般所定义，R^6的各实例独立地是R^A或R^B，其中R^6经q个R^C实例取代；或两个R^6实例、一个R^6实例及一个R^L实例、一个R^6实例及一个R^{WA}实例，或一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至8元部分不饱和或芳香族环；其中所述环经r个R^C实例取代。

[0158] 在一些实施例中，两个R^6实例、一个R^6实例及一个R^L实例、一个R^6实例及一个R^{WA}实例，或一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至8元部分不饱和或芳香族环；其中所述环经r个R^C实例取代。

[0159] 在一些实施例中，一个R^6实例及一个R^{WA}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至8元部分不饱和或芳香族环；其中所述环经r个R^C实例取代。在一些实施例中，一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至8元部分不饱和或芳香族环；其中所述环经r个R^C实例取代。

[0160] 在一些实施例中，一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至8元部分不饱和或芳香族环；其中所述环经r个R^C实例取代。在一些实施例中，一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有一个氮原子的4至8元部分不饱和环；其中所述环任选地经1、2或3个独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-(C_{1-4}烷基)的取代基取代；其中各C_{1-4}烷基任选地经1、2或3个氟取代。在一些实施例中，一个R^6实例及一个R^{7a}实例与其间插原子一起形成4至8元部分不饱和环。在一些实施例中，一个R^6实例及一个R^{7a}实例与其间插原子一起形成具有一个氮原子的4至8元部分不饱和环。

[0161] 在一些实施例中，各R^6是选自表1的化合物中所描绘的基团。

[0162] 如上文一般所定义，R^8是H、$-NR_2$、卤素、-OH，或任选地经1至3个卤素取代的C_{1-6}脂肪族。在一些实施例中，R^8是H。在一些实施例中，R^8是$-NR_2$。在一些实施例中，R^8是卤素。在一些实施例中，R^8是-OH。在一些实施例中，R^8是任选地经1至3个卤素取代的C_{1-6}脂肪族。

[0163] 在一些实施例中，R^8是$-NH_2$。在一些实施例中，R^8是C_{1-4}烷基。在一些实施例中，R^8是甲基。在一些实施例中，R^8是$-NH_2$或甲基。在一些实施例中，R^8是选自表1中的化合物中所描绘的基团。

[0164] 如上文一般所定义，R^9是H、$-NR_2$、卤素，或任选地经1至3个卤素取代的C_{1-6}脂肪族。在一些实施例中，R^9是H。在一些实施例中，R^9是$-NR_2$。在一些实施例中，R^9是$-NH_2$。在一些实施例中，R^9是卤素。在一些实施例中，R^9是任选地经1至3个卤素取代的C_{1-6}脂肪族。在一些实施

例中,R^9是C_{1-4}烷基。在一些实施例中,R^9是选自表1中的化合物中所描绘的基团。

[0165] 如上文一般所定义,R^{10}是H或任选地经1至3个卤素取代的C_{1-6}脂肪族。在一些实施例中,R^{10}是H。在一些实施例中,R^{10}是任选地经1至3个卤素取代的C_{1-6}脂肪族。在一些实施例中,R^{10}是C_{1-4}烷基。在一些实施例中,R^{10}是甲基。在一些实施例中,R^{10}是H或甲基。在一些实施例中,R^{10}是选自表1中的化合物中所描绘的基团。

[0166] 如上文一般所定义,L^6为共价键,或C_{1-4}饱和或不饱和、直链或分支链二价烃链,其中所述链的一或两个亚甲基单元任选地且独立地经以下置换:-CH(R^L)-、-C(R^L)$_2$-、C_{3-6}亚环烷基、3至6元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-;其中所述C_{3-6}亚环烷基、3至6元亚杂环烷基及5至6元亚杂芳基中的每一者任选地经一个R^A或C_{1-6}脂肪族实例取代。

[0167] 在一些实施例中,L^6是C_{3-6}亚环烷基、3至6元亚杂环烷基,或5至6元亚杂芳基,其中的每一者任选地经一个R^A或C_{1-6}脂肪族实例取代。在一些实施例中,L^6是C_{3-6}亚环烷基、3至6元亚杂环烷基,或5至6元亚杂芳基。

[0168] 在一些实施例中,L^6是选自表1的化合物中所描绘的基团。

[0169] 如上文一般所定义,R^{5C}及R^{5D}的各实例独立地是R^A或R^B,且经u个R^C实例取代;或两个R^{5C}实例、一个R^{5C}实例及一个R^{5D}实例,或两个R^{5D}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的3至7元饱和、部分不饱和或芳香族环;其中所述环经v个R^C实例取代。

[0170] 在一些实施例中,两个R^{5C}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的3至7元饱和、部分不饱和或芳香族环;其中所述环经v个R^C实例取代。

[0171] 在一些实施例中,一个R^{5C}实例及一个R^{5D}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的3至7元饱和、部分不饱和或芳香族环;其中所述环经v个R^C实例取代。在一些实施例中,一个R^{5C}实例及一个R^{5D}实例与其间插原子一起形成经v个R^C实例取代的3至7元饱和或部分不饱和碳环。

[0172] 在一些实施例中,两个R^{5D}实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的3至7元饱和、部分不饱和或芳香族环;其中所述环经v个R^C实例取代。在一些实施例中,两个R^{5D}实例与其间插原子一起形成经v个R^C实例取代的3至7元饱和或部分不饱和碳环。

[0173] 在一些实施例中,R^{5C}及R^{5D}的各实例是选自表1的化合物中所描绘的基团。

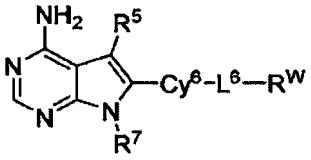
[0174] 如上文一般所定义,v是0、1、2、3或4。在一些实施例中,v是0。在一些实施例中,v是1。在一些实施例中,v是2。在一些实施例中,v是3。在一些实施例中,v是4。在一些实施例中,v是0或1。在一些实施例中,v是0、1或2。在一些实施例中,v是0、1、2或3。在一些实施例中,v是1或2。在一些实施例中,v是1、2或3。在一些实施例中,v是1、2、3或4。在一些实施例中,v是2或3。在一些实施例中,v是2、3或4。在一些实施例中,v是3或4。在一些实施例中,v是选自表1中的化合物所示的值。

[0175] 如上文一般所定义,w是0、1、2、3或4。在一些实施例中,w是0。在一些实施例中,w是1。在一些实施例中,w是2。在一些实施例中,w是3。在一些实施例中,w是4。在一些实施例中,w是0或1。在一些实施例中,w是0、1或2。在一些实施例中,w是0、1、2或3。在一些实施例中,w

是1或2。在一些实施例中,w是1、2或3。在一些实施例中,w是1、2、3或4。在一些实施例中,w是2或3。在一些实施例中,w是2、3或4。在一些实施例中,w是3或4。在一些实施例中,w是选自表1中的化合物所示的值。

[0176] 在一些实施例中,本发明提供式I-1化合物,其中各变量如以下式I或式I-2的描述中所定义且以单独及组合形式描述于本文实施例中。

[0177] 如上文所述,在一些实施例中,本发明提供式I-2化合物:

[0178] 

I-2

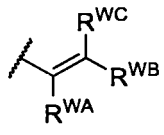
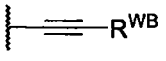
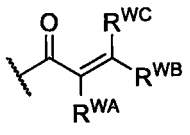
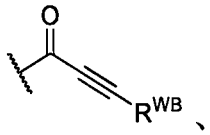
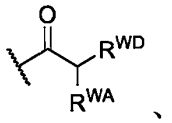
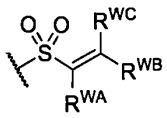
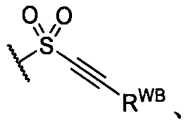
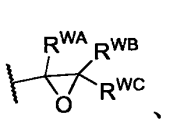
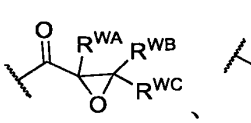
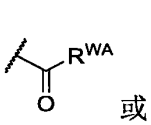
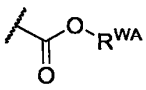
[0179] 或其药学上可接受的盐,其中:

[0180] R^5是-R^{5A}-L^5-R^{5B};

[0181] R^{5A}是R^B的二价基团,其中除-L^5-R^{5B}之外,R^{5A}还经m个R^{5C}实例取代;

[0182] R^{5B}是氢或R^B,其中R^{5B}经n个R^{5D}实例取代;

[0183] Cy^6是亚苯基或具有1至3个氮原子的6元亚杂芳基,其中除-L^6-R^W之外,Cy^6还经p个R^6实例取代;

[0184] R^W是卤素、-CN、  、  、  、  、  、  、  、  、  、  或  ;

[0185] R^6的各实例独立地是R^A或R^B,其中R^6经q个R^C实例取代;或

[0186] 两个R^6实例,或一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环;其中所述环经r个R^C实例取代;

[0187] R^7是H或R^B,其中R^7经t个R^{7A}实例取代;

[0188] L^5及L^6中的每一者独立地是共价键,或C_{1-4}饱和或不饱和、直链或分支链二价烃链,其中所述链的一或两个亚甲基单元任选地且独立地经以下置换:-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)2-;

[0189] R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;或

[0190] R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^{L}实例,或R^{WC}及一个R^{L}实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环;

[0191] R^{WD}是卤素或-OS(O)$_2$R;

[0192] R^{5C}、R^{5D}、R^{7A}及R^{L}的各实例独立地是R^{A}或R^{B},且经u个R^{C}实例取代;

[0193] R^{A}的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$或-N(R)S(O)$_2$R;

[0194] R^{B}的各实例独立地是C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;或具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环;

[0195] R^{C}的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-S(O)$_2$F、-OS(O)$_2$F、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R,或选自以下的任选地经取代的基团:$C_{1-6}$脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;

[0196] 各R独立地是氢或选自以下的任选地经取代的基团:C_{1-6}脂肪族;苯基;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环;及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环,或:

[0197] 同一氮上的两个R基团与其间插原子一起形成4至7元饱和、部分不饱和或杂芳基环,除所述氮之外,所述环还具有0至3个独立地选自氮、氧及硫的杂原子;及

[0198] m、n、p、q、r、t及u中的每一者独立地是0、1、2、3或4。

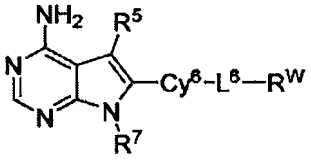
[0199] 如上文一般所定义,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;或R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^{L}实例,或R^{WC}及一个R^{L}实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环。

[0200] 在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2或-C(O)N(R)OR。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘或任选地经取代的C_{1-6}脂肪族。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘、-C_{1-4}烷基、-(C_{1-4}烷基)-O-(C_{1-4}烷基),或-(C_{1-4}烷基)-N(C_{1-4}烷基)$_2$;其中各C_{1-4}烷基任选地经1、2或3个氟取代。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘,或任选地经1、2或3个氟取代的-C_{1-4}烷基。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘或-C_{1-4}烷基。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘或-CH_3。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢或氘。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者是氘。

[0201] 在一些实施例中,本发明提供式I-2化合物,其中各变量如以下式I的描述中所定

义且以单独及组合形式描述于本文实施例中。

[0202] 如上文所述,在一些实施例中,本发明提供式I化合物:

[0203] 

I

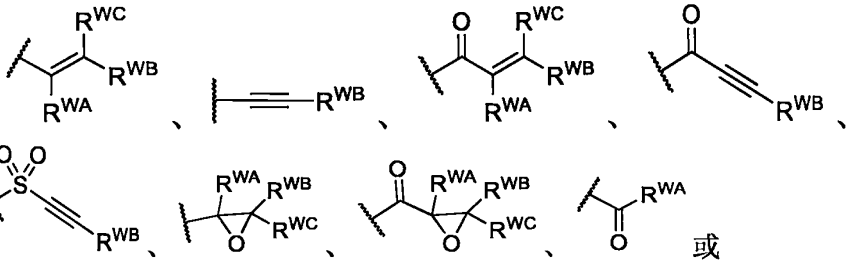
[0204] 或其药学上可接受的盐,其中:

[0205] R^5是-R^{5A}-L^5-R^{5B};

[0206] R^{5A}是R^B之二价基团,其中除-L^5-R^{5B}之外,R^{5A}还经m个R^{5C}实例取代;

[0207] R^{5B}是氢或R^B,其中R^{5B}经n个R^{5D}实例取代;

[0208] Cy^6是亚苯基或具有1至3个氮原子的6元亚杂芳基,其中除-L^6-R^W之外,Cy^6还经p个R^6实例取代;

[0209] R^W是卤素、-CN、 

;

[0210] R^6的各实例独立地是R^A或R^B,其中R^6经q个R^C实例取代;或

[0211] 两个R^6实例,或一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环;其中所述环经r个R^C实例取代;

[0212] R^7是H或R^B,其中R^7经t个R^{7A}实例取代;

[0213] L^5及L^6中的每一者独立地是共价键,或C_{1-4}饱和或不饱和、直链或分支链二价烃链,其中所述链的一或两个亚甲基单元任选地且独立地经以下置换:-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-;

[0214] R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;或

[0215] R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例,或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环;

[0216] R^{WD}是卤素或-OS(O)$_2$R;

[0217] R^{5C}、R^{5D}、R^{7A}及R^L的各实例独立地是R^A或R^B,且经u个R^C实例取代;

[0218] R^A的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-$S(O)_2R$、-$S(O)_2NR_2$、-S(O)R、-$S(O)NR_2$、-C(O)R、-C(O)OR、-$C(O)NR_2$、-C(O)N(R)OR、-OC(O)R、-$OC(O)NR_2$、-N(R)C(O)OR、-N(R)C(O)R、-$N(R)C(O)NR_2$、-$N(R)C(NR)NR_2$、-$N(R)S(O)_2NR_2$或-$N(R)S(O)_2R$;

[0219] R^B的各实例独立地是C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;或具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环;

[0220] R^C的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-$S(O)_2R$、-$S(O)_2NR_2$、-S(O)R、-$S(O)NR_2$、-$S(O)_2F$、-OS(O)$_2$F、-C(O)R、-C(O)OR、-$C(O)NR_2$、-C(O)N(R)OR、-OC(O)R、-$OC(O)NR_2$、-N(R)C(O)OR、-N(R)C(O)R、-$N(R)C(O)NR_2$、-$N(R)C(NR)NR_2$、-$N(R)S(O)_2NR_2$、-$N(R)S(O)_2R$,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;

[0221] 各R独立地是氢或选自以下的任选地经取代的基团:C_{1-6}脂肪族;苯基;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环;及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环,或:

[0222] 同一氮上的两个R基团与其间插原子一起形成4至7元饱和、部分不饱和或杂芳基环,除所述氮之外,所述环还具有0至3个独立地选自氮、氧及硫的杂原子;及

[0223] m、n、p、q、r、t及u中的每一者独立地是0、1、2、3或4。

[0224] 如上文一般所定义,R^{5A}是R^B的二价基团,其中除-L^5-R^{5B}之外,R^{5A}还经m个$R5^C$实例取代;在一些实施例中,R^{5A}为二价C_1-$_6$脂肪族,除-L^5-R^{5B}之外,其还经m个R^{5C}实例取代。在一些实施例中,R^{5A}是亚苯基,除-L^5-R^{5B}之外,其还经m个R^{5C}实例取代。在一些实施例中,R^{5A}是具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环亚杂芳基环,除-L^5-R^{5B}之外,所述环还经m个R^{5C}实例取代。在一些实施例中,R^{5A}是具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环亚杂芳基环,除-L^5-R^{5B}之外,所述环还经m个R^{5C}实例取代。在一些实施例中,R^{5A}是3至7元饱和或部分不饱和二价碳环,除-L^5-R^{5B}之外,所述碳环还经m个R^{5C}实例取代。在一些实施例中,R^{5A}是具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和二价单环杂环,除-L^5-R^{5B}之外,所述单环杂环还经m个R^{5C}实例取代。在一些实施例中,R^{5A}是具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和二价双环杂环,除-L^5-R^{5B}之外,所述双环杂环还经m个R^{5C}实例取代。在一些实施例中,R^{5A}是选自表1的化合物中所描绘的基团。

[0225] 如上文一般所定义,L^5为共价键,或C_{1-4}饱和或不饱和、直链或分支链二价烃链,其中所述链的一或两个亚甲基单元任选地且独立地经以下置换:-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-。在一些实施例中,L^5为共价键。在一些实施例中,L^5是C_{1-4}饱和或不饱和、直链或分支链二价烃链,其中所述链的一或两个亚甲基单元任选地且独立地经以下置换:-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-

NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-。

[0226] 在一些实施例中，L^5是C_{1-2}饱和或不饱和、直链或分支链二价烃链，其中所述链的一或两个亚甲基单元任选地且独立地经以下置换：-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-。在一些实施例中，L^5是C_{1-2}饱和或不饱和、直链或分支链二价烃链，其中所述链的一或两个亚甲基单元任选地且独立地经-O-、-C(O)-、-C(O)NH-或-C(O)N(R^L)-置换。

[0227] 在一些实施例中，L^5是-O-、-C(O)-、-C(O)NH-或-C(O)N(R^L)-。在一些实施例中，L^5是-O-。在一些实施例中，L^5是-C(O)-。在一些实施例中，L^5是-C(O)NH-。在一些实施例中，L^5是-C(O)N(R^L)-。在一些实施例中，L^5是选自表1的化合物中所描绘的基团。

[0228] 如上文一般所定义，R^{5B}为氢或R^B，其中R^{5B}经n个R^{5D}实例取代。在一些实施例中，R^{5B}为氢。在一些实施例中，R^{5B}是经n个R^{5D}实例取代的R^B。在一些实施例中，R^{5B}是经n个R^{5D}实例取代的C_{1-6}脂肪族。在一些实施例中，R^{5B}是经n个R^{5D}实例取代的苯基。在一些实施例中，R^{5B}是具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环，其经n个R^{5D}实例取代。在一些实施例中，R^{5B}是具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环，其经n个R^{5D}实例取代。在一些实施例中，R^{5B}为经n个R^{5D}实例取代的3至7元饱和或部分不饱和碳环。在一些实施例中，R^{5B}是具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环，所述单环杂环经n个R^{5D}实例取代。在一些实施例中，R^{5B}是具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环，所述双环杂环经n个R^{5D}实例取代。

[0229] 在一些实施例中，R^{5B}是具有1至2个独立地选自氮、氧及硫的杂原子的4至6元饱和或部分不饱和单环杂环，所述单环杂环经n个R^{5D}实例取代。在一些实施例中，R^{5B}是具有1至3个独立地选自氮、氧及硫的杂原子的5元单环杂芳基环，所述单环杂芳基环经n个R^{5D}实例取代。在一些实施例中，R^{5B}是具有1至2个独立地选自氮、氧及硫的杂原子的6元单环杂芳基环，所述单环杂芳基环经n个R^{5D}实例取代。在一些实施例中，R^{5B}选自表1的化合物中所描绘的基团。

[0230] 如上文一般所定义，R^{5C}的各实例独立地是R^A或R^B，且经u个R^C实例取代。在一些实施例中，R^{5C}的各实例是R^A。在一些实施例中，R^{5C}的各实例独立地选自卤素、-CN、-OR、-S(O)$_2$NR_2、-C(O)R、-C(O)OR、-C(O)NR_2、-OC(O)R及-N(R)C(O)R。在一些实施例中，R^{5C}的各实例独立地选自卤素、-CN、-OR及-C(O)NR_2。在-些实施例中，R^{5C}的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-C(O)N(C_{1-4}烷基)$_2$；其中各C_{1-4}烷基任选地经1、2或3个卤素取代。在一些实施例中，R^{5C}的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-C(O)N(C_{1-4}烷基)$_2$。

[0231] 在一些实施例中，R^{5C}的各实例为R^B，其中R^{5C}经u个R^C实例取代。在一些实施例中，R^{5C}的各实例是R^B，其中R^{5C}经一个R^C实例取代。在一些实施例中，R^{5C}的各实例独立地选自C_{1-6}脂肪族；苯基；具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环；3至7元饱和或部分不饱和碳环；具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环；其中的每一者任选地经u个R^C实例取代。

[0232] 在一些实施例中,R^{5C}的各实例独立地选自C_{1-6}脂肪族;3至7元饱和或部分不饱和碳环;及具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;其中的每一者任选地经u个R^{C}实例取代。在一些实施例中,R^{5C}的各实例独立地选自:任选地经一个R^{C}实例取代的C_{1-4}脂肪族;3至5元饱和碳环;及具有1个独立地选自氮、氧及硫的杂原子的3至5元饱和单环杂环;其中的每一者任选地经1、2或3个卤素取代。在一些实施例中,R^{5C}的各实例独立地选自:任选地经-OH、-O-(C_{1-4}烷基)或-N(C_{1-4}烷基)$_2$的一个实例取代的C_{1-4}烷基;3至5元饱和碳环;及具有1个氧原子的3至5元饱和单环杂环;其中的每一者任选地经1、2或3个氟或氯取代。

[0233] 在一些实施例中,R^{5C}的各实例独立地选自卤素、-CN、-OR、-C(O)NR_2,及以下基团(其中的每一者任选地经u个R^{C}实例取代):C_{1-6}脂肪族;3至7元饱和或部分不饱和碳环;及具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环。在一些实施例中,R^{5C}的各实例独立地选自卤素、-CN,及以下基团(其中的每一者任选地经1、2或3个卤素取代):-O-(C_{1-4}烷基)、-C(O)N(C_{1-4}烷基)$_2$、任选地经一个R^{C}实例取代的C_{1-4}脂肪族;3至5元饱和碳环;及具有1个独立地选自氮、氧及硫的杂原子的3至5元饱和单环杂环。在一些实施例中,R^{5C}的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)、-C(O)N(C_{1-4}烷基)$_2$及以下基团(其中的每一者任选地经1、2或3个氟或氯取代):任选地经-OH、-O-(C_{1-4}烷基)或-N(C_{1-4}烷基)$_2$的一个实例取代的C_{1-4}烷基;3至5元饱和碳环;及具有1个氧原子的3至5元饱和单环杂环。在一些实施例中,R^{5C}是选自表1的化合物中所描绘的基团。

[0234] 如上文一般所定义,R^{5D}的各实例独立地是R^{A}或R^{B},且经$_u$个R^{C}实例取代。在一些实施例中,R^{5D}的各实例为R^{A}。在一些实施例中,R^{5D}的各实例独立地选自卤素、-CN、-OR、-S(O)$_2NR_2$、-C(O)R、-C(O)OR、-C(O)NR_2、-OC(O)R,及-N(R)C(O)R。在一些实施例中,R^{5D}的各实例独立地选自卤素、-CN、-OR及-C(O)NR_2。在一些实施例中,R^{5D}的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-C(O)N(C_{1-4}烷基)$_2$;其中各C_{1-4}烷基任选地经1、2或3个卤素取代。在一些实施例中,R^{5D}的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-C(O)N(C_{1-4}烷基)$_2$。

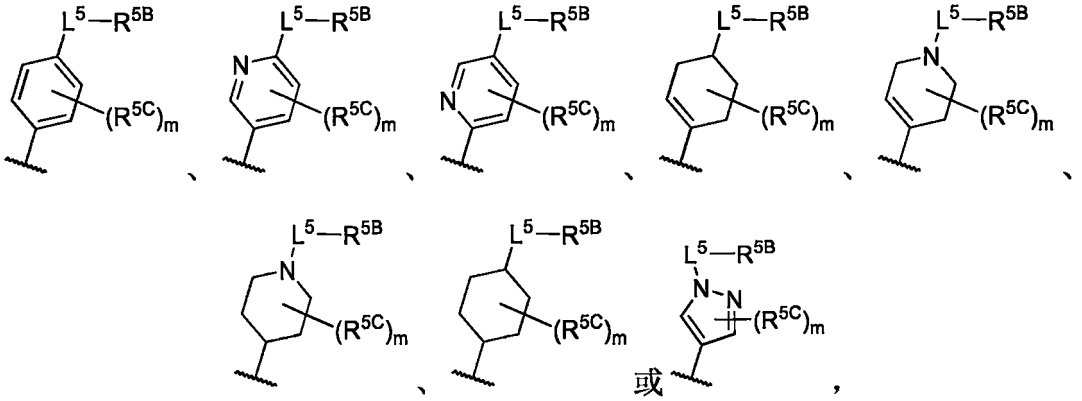
[0235] 在一些实施例中,R^{5D}的各实例是R^{B},其中R^{5D}经u个R^{C}实例取代。在一些实施例中,R^{5D}的各实例是R^{B},其中R^{5D}经一个R^{C}实例取代。在一些实施例中,R^{5D}的各实例独立地选自C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;其中的每一者任选地经u个R^{C}实例取代。

[0236] 在一些实施例中,R^{5D}的各实例独立地选自C_{1-6}脂肪族;3至7元饱和或部分不饱和碳环;及具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;其中的每一者任选地经u个R^{C}实例取代。在一些实施例中,R^{5D}的各实例独立地选自:任选地经一个R^{C}实例取代的C_{1-4}脂肪族;3至5元饱和碳环;及具有1个独立地选自氮、氧及硫的杂原子的3至5元饱和单环杂环;其中的每一者任选地经1、2或3个卤素取代。在一些实施例中,R^{5D}的各实例独立地选自:任选地经-OH、-O-(C_{1-4}烷基)或-N(C_{1-4}烷基)$_2$的一个实例取代的C_{1-4}烷基;3至5元饱和碳环;及具有1个氧原子的3至5元饱和单环杂环;其中的每一者任选地经1、2或3个氟或氯取代。

[0237] 在一些实施例中,R^{5D}的各实例独立地选自卤素、-CN、-OR、-C(O)NR_2,及以下基团(其中的每一者任选地经u个R^{C}实例取代):C_{1-6}脂肪族;3至7元饱和或部分不饱和碳环;及具

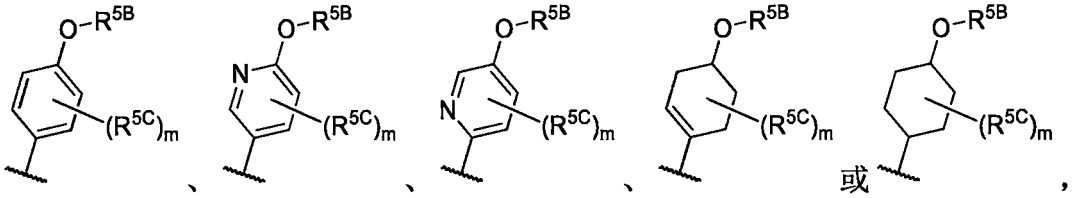
有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环。在一些实施例中,R^{5D}的各实例独立地选自卤素、-CN,及以下基团(其中的每一者任选地经1、2或3个卤素取代):-O-(C_{1-4}烷基)、-C(O)N(C_{1-4}烷基)$_2$、任选地经一个R^C实例取代的C_{1-4}脂肪族;3至5元饱和碳环;及具有1个独立地选自氮、氧及硫的杂原子的3至5元饱和单环杂环。在一些实施例中,R^{5D}的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)、-C(O)N(C_{1-4}烷基)$_2$及以下基团(其中的每一者任选地经1、2或3个氟或氯取代):任选地经-OH、-O-(C_{1-4}烷基)或-N(C_{1-4}烷基)$_2$的一个实例取代的C_{1-4}烷基;3至5元饱和碳环;及具有1个氧原子的3至5元饱和单环杂环。在一些实施例中,R^{5D}是选自表1的化合物中所描绘的基团。

[0238] 如上文一般所定义,在一些实施例中,本发明提供式I化合物,其中R^5是-R^{5A}-L^5-R^{5B}。在一些实施例中,R^5(即,-R^{5A}-L^5-R^{5B}结合在一起)是:

[0239] 

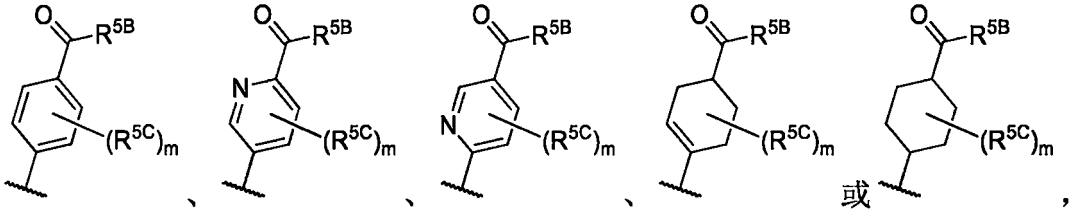
[0240] 其中L^5、R^{5B}、R^{5C}及m中的每一者如在实施例以及本文的类别及子类中所定义。

[0241] 在一些实施例中,R^5(即,-R^{5A}-L^5-R^{5B}结合在一起)是:

[0242] 

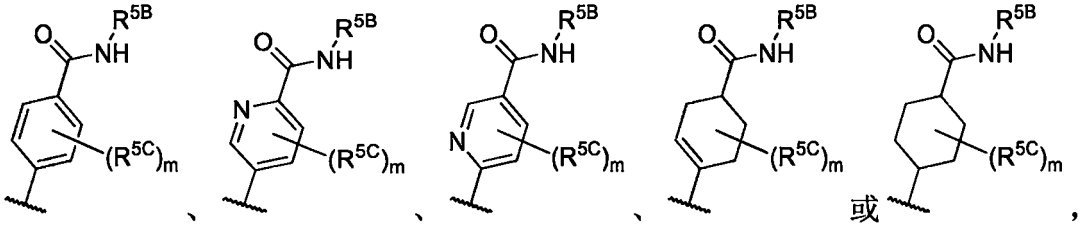
[0243] 其中R^{5B}、R^{5C}及m中的每一者如本文的实施例以及各类别及子类中所定义。

[0244] 在一些实施例中,R^5(即,-R^{5A}-L^5-R^{5B}结合在一起)是:

[0245] 

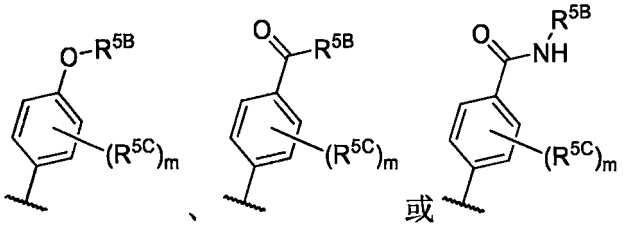
[0246] 其中R^{5B}、R^{5C}及m中的每一者如本文的实施例以及各类别及子类中所定义。

[0247] 在一些实施例中,R^5(即,-R^{5A}-L^5-R^{5B}结合在一起)是:

[0248] 

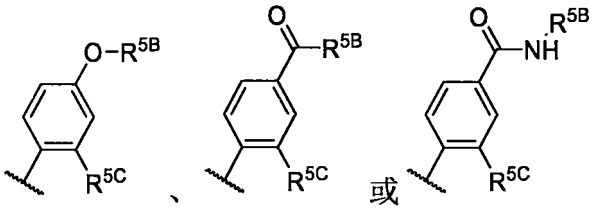
[0249] 其中R^{5B}、R^{5C}及m中的每一者如本文的实施例以及各类别及子类中所定义。

[0250] 在一些实施例中,R^5(即,$-R^{5A}-L^5-R^{5B}$结合在一起)是:

[0251] 

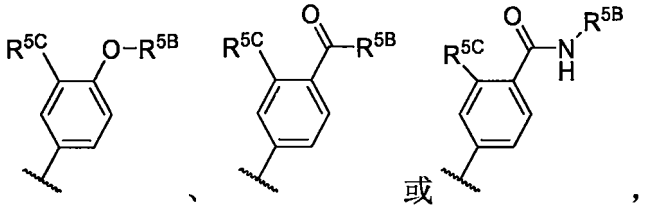
[0252] 其中R^{5B}、R^{5C}及m中的每一者如本文的实施例以及各类别及子类中所定义。

[0253] 在一些实施例中,R^5(即,$-R^{5A}-L^5-R^{5B}$结合在一起)是:

[0254] 

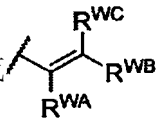
[0255] 其中R^{5B}及R^{5C}中的每一者如本文的实施例以及各类别及子类中所定义。

[0256] 在一些实施例中,R^5(即,$-R^{5A}-L^5-R^{5B}$结合在一结合)是:

[0257] 

[0258] 其中R^{5B}及R^{5C}中的每一者如本文的实施例以及各类别及子类中所定义。

[0259] 在一些实施例中,R^5(即,$-R^{5A}-L^5-R^{5B}$结合在一起)是选自表1的化合物中所描绘的基团。

[0260] Cy^6为亚苯基或具有1至3个氮原子的6元亚杂芳基,其中除$-L^6-R^W$之外,Cy^6还经p个R^6实例取代。在一些实施例中,Cy^6为亚苯基,除$-L^6-R^W$之外,其还经p个R^6实例取代。在一些实施例中,Cy^6是具有1至3个氮原子的6元亚杂芳基;其中除$-L^6-R^W$之外,Cy^6还经p个R^6实例取代。在一些实施例中,Cy^6是具有1至2个氮原子的6元亚杂芳基,除$-L^6-R^W$之外,其还经p个R^6实例取代。在一些实施例中,Cy^6是具有1个氮原子的6元亚杂芳基,除$-L^6-R^W$之外,其还经p个R^6实例取代。在一些实施例中,Cy^6是具有2个氮原子的6元亚杂芳基,除$-L^6-R^W$之外,其还经p个R^6实例取代。在一些实施例中,Cy^6是具有2个氮原子的6元亚杂芳基,其仅经$-L^6-R^W$取代。在一些实施例中,Cy^6是具有1至2个氮原子的6元亚杂芳基,除$-L^6-R^W$之外,其还经p个R^6实例取代,其中L^6是共价键,且$-R^W$是-CN或  在一些实施例中,Cy^6是选自表1的化合物中所描绘的基团。

[0261] 如上文一般所定义,R^6的各实例独立地是R^A或R^B,其中R^6经q个R^C实例取代;或两个R^6实例,或一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环;其中所述环经r个R^C实例取代。在一些实施例中,R^6的各实例独立地是R^A或R^B,其中R^6经q个R^C实例取代。

[0262] 在一些实施例中,两个R^6实例,或一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环;其中所述环经r个R^C实例取代。在一些实施例中,两个R^6实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环;其中所述环经r个R^C实例取代。

[0263] 在一些实施例中,一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环;其中所述环经r个R^C实例取代。在一些实施例中,一个R^6实例及一个R^L实例与其间插原子一起形成具有一个氮原子的4至7元部分不饱和环;其中所述环任选地经1、2或3个独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-(C_{1-4}烷基)之取代基取代;其中各C_{1-4}烷基任选地经1、2或3个氟取代。在一些实施例中,一个R^6实例及一个R^L实例与其间插原子一起形成具有一个氮原子的4至7元部分不饱和环。

[0264] 在一些实施例中,R^6的各实例是R^A。在一些实施例中,R^6的各实例独立地选自卤素、-CN、-OR、-S(O)$_2$NR$_2$、-C(O)R、-C(O)OR、-C(O)NR$_2$、-OC(O)R,及-N(R)C(O)R。在一些实施例中,R^6的各实例独立地选自卤素、-CN、-OR及-C(O)NR$_2$。在一些实施例中,R^6的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-C(O)N(C_{1-4}烷基)$_2$;其中各C_{1-4}烷基任选地经1、2或3个卤素取代。在一些实施例中,R^6的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)及-C(O)N(C_{1-4}烷基)$_2$。

[0265] 在一些实施例中,R^6的各实例为R^B,其中R^6经q个R^C实例取代。在一些实施例中,R^6的各实例为R^B,其中R^6经一个R^C实例取代。在一些实施例中,R^6的各实例独立地选自C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;其中的每一者任选地经q个R^C实例取代。

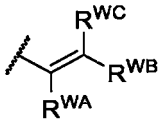
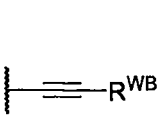
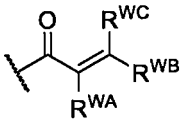
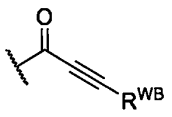
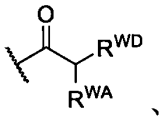
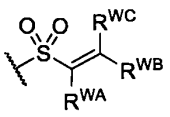
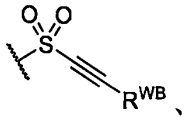
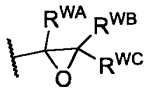
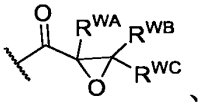
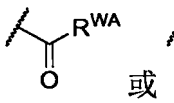
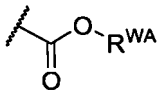
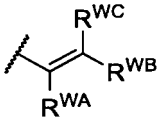
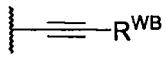
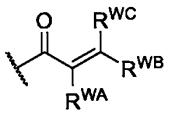
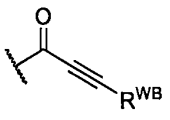
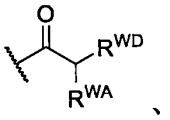
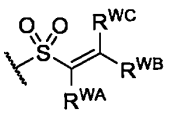
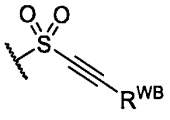
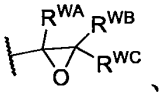
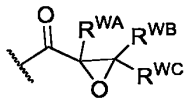
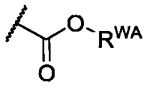
[0266] 在一些实施例中,R^6的各实例独立地选自C_{1-6}脂肪族;3至7元饱和或部分不饱和碳环;及具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;其中的每一者任选地经q个R^C实例取代。在一些实施例中,R^6的各实例独立地选自:任选地经一个R^C实例取代的C_{1-4}脂肪族;3至5元饱和碳环;及具有1个独立地选自氮、氧及硫的杂原子的3至5元饱和单环杂环;其中的每一者任选地经1、2或3个卤素取代。在一些实施例中,R^6的各实例独立地选自:任选地经-OH、-O-(C_{1-4}烷基)或-N(C_{1-4}烷基)$_2$的一个实例取代的C_{1-4}烷基;3至5元饱和碳环;及具有1个氧原子的3至5元饱和单环杂环;其中的每一者任选地经1、2或3个氟或氯取代。

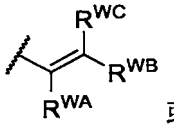
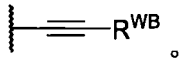
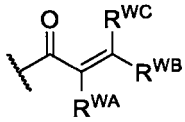
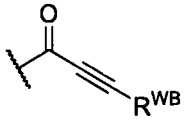
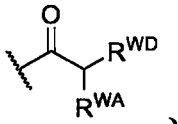
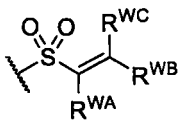
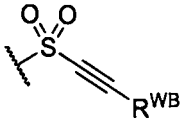
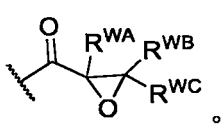
[0267] 在一些实施例中,R^6的各实例独立地选自卤素、-CN、-OR、-C(O)NR$_2$,及以下基团(其中的每一者任选地经q个R^C实例取代):C_{1-6}脂肪族;3至7元饱和或部分不饱和碳环;及具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环。在一些实施例中,R^6的各实例独立地选自卤素、-CN,及以下基团(其中的每一者任选地经1、2或3个卤素取代):-O-(C_{1-4}烷基)、-C(O)N(C_{1-4}烷基)$_2$、任选地经一个R^C实例取代的C_{1-4}脂肪族;3至5元饱和碳环;及具有1个独立地选自氮、氧及硫的杂原子的3至5元饱和单环杂环。在一些实施例中,R^6的各实例独立地选自卤素、-CN、-O-(C_{1-4}烷基)、-C(O)N(C_{1-4}烷基)$_2$及以下基团(其中的每一者任选地经1、2或3个氟或氯取代):任选地经-OH、-O-(C_{1-4}烷基)或-N(C_{1-4}烷基)$_2$的一个实例取代的C_{1-4}烷基;3至5元饱和碳环;及具有1个氧原子的3至5元饱和单环杂环。在一些实施例中,R^6是选自表1的化合物中所描绘的基团。

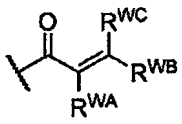
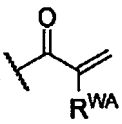
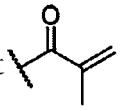
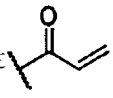
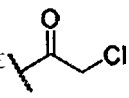
[0268] 如上文一般所定义，L^6是共价键，或C_{1-4}饱和或不饱和、直链或分支链二价烃链，其中所述链的一或两个亚甲基单元任选地且独立地经以下置换：-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-。在一些实施例中，L^6是共价键。在一些实施例中，L^6是C_{1-4}饱和或不饱和、直链或分支链二价烃链，其中所述链的一或两个亚甲基单元任选地且独立地经以下置换：-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-。

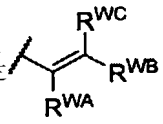
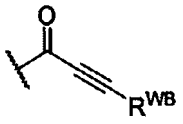
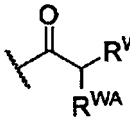
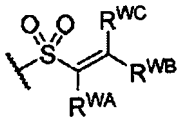
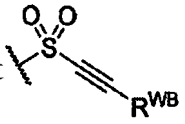
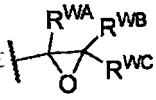
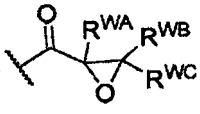
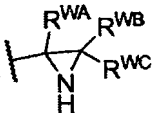
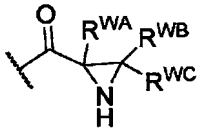
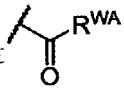
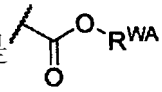
[0269] 在一些实施例中，L^6是C_{1-2}饱和或不饱和、直链或分支链二价烃链，其中所述链的一或两个亚甲基单元任选地且独立地经以下置换：-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-。在一些实施例中，L^6是C_{1-2}饱和或不饱和、直链或分支链二价烃链，其中所述链的一个亚甲基单元任选地经-NH-或-N(R^L)-置换。

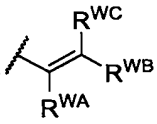
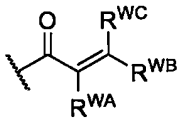
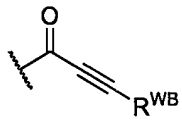
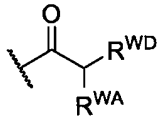
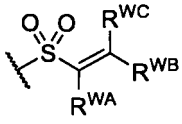
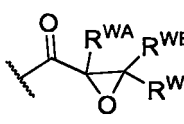
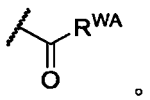
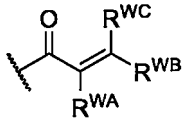
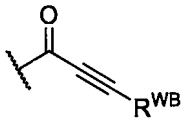
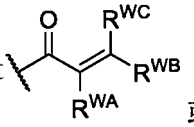
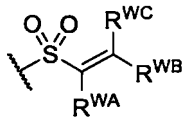
[0270] 在一些实施例中，L^6是-NH-或-N(R^L)-。在一些实施例中，L^6是-NH-。在一些实施例中，L^6是-N(R^L)-。在一些实施例中，L^6是-NH-或-N(CH_3)-。在一些实施例中，L^6是-N(CH_3)-。在一些实施例中，L^6是选自表1的化合物中所描绘的基团。

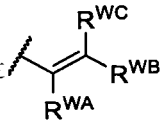
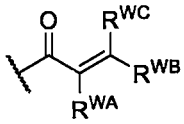
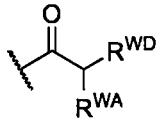
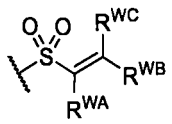
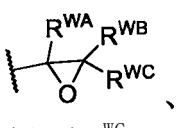
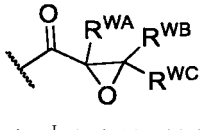
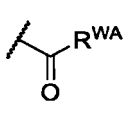
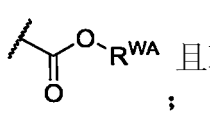
[0271] 如上文一般所定义，R^W是卤素、-CN、  、  、  、  、  、  、  、  、  、  或  。在一些实施例中，R^W是卤素、-CN、  、  、  、  、  、  、  、  、  或  。

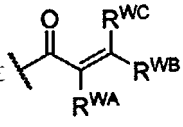
[0272] 在一些实施例中，R^W是卤素。在一些实施例中，R^W是-CN。在一些实施例中，R^W是  或  。在一些实施例中，R^W是  、  、  、  、  或  。在一些实施例中，R^W是

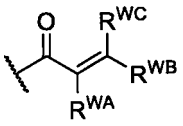
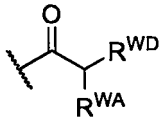
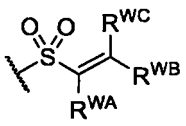
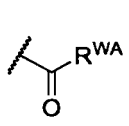
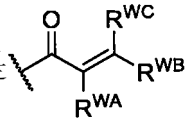
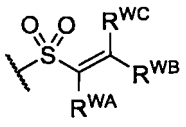
 在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是 

[0273] 在一些实施例中,R^W是  在一些实施例中,R^W是 在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是  在一些实施例中,R^W是 

[0274] 在一些实施例中,R^W是-CN、  、  、  、  、  、  或  。在一些实施例中,R^W是  或  。在一些实施例中,R^W是  或  。

[0275] 在一些实施例中,R^W是  、  、  、  、  、  、  或  ;且R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例,或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环。

[0276] 在一些实施例中,R^W是  且R^{WA}及R^{WB}或R^{WB}及R^{WC}与其间插原子一起形成具,

有0至1个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和环。在一些实施例中，R^W是  、  、  、  ；且R^{WA}及一个R^L实例与其间插原子一起形成具有0至1个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环。在一些实施例中，R^W是  或  ，且R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和环。在一些实施例中，R^W是选自表1的化合物中所描绘的基团。

[0277] 不希望受任何特定理论束缚，咸信R^W是弹头基团，尤其适于共价结合至蛋白激酶之硫氢基侧链部分，例如FGFR2之Cys491。因此，在一些实施例中，R^W的特征在于其能够共价结合至半胱氨酸残基，从而不可逆地抑制蛋白激酶。在一些实施例中，蛋白激酶为FGFR。在某些实施例中，蛋白激酶为FGFR2。在某些实施例中，蛋白激酶为FGFR2，且半胱氨酸残基是Cys491。

[0278] 如上文一般所定义，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR，或选自以下的任选地经取代的基团：C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环，及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环；或R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例，或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环。

[0279] 在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR，或选自以下的任选地经取代的基团：C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环，及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环。在一些实施例中，R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例，或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环。

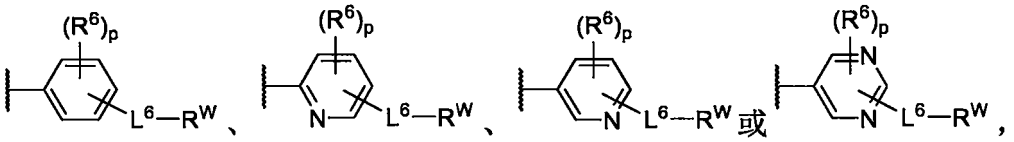
[0280] 在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2，或-C(O)N(R)OR。在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是选自以下的任选地经取代的基团：C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环，及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环。

[0281] 在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢或任选地经取代的C_{1-6}脂肪族。在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢或任选地经取代的C_{1-6}脂肪族。在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、-C_{1-4}烷基、-(C_{1-4}烷基)-O-(C_{1-4}烷基)，或-(C_{1-4}烷基)-N(C_{1-4}烷基)$_2$；其中各C_{1-4}烷基任选地经1、2或3个氟取代。在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢或任选地经1、2或3个氟取代的-C_{1-4}烷基。在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢或-C_{1-4}烷基。在一些实施例中，R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢或-CH_3。

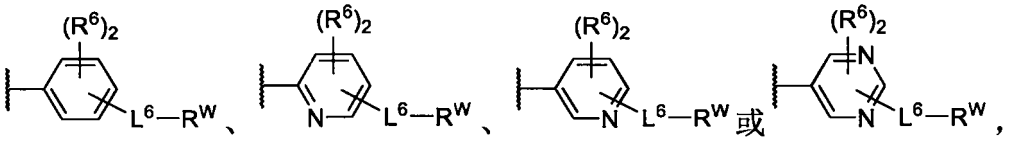
[0282] 在一些实施例中,R^{WA}及R^{WB}或R^{WB}及R^{WC}与其间插原子一起形成具有0至1个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和环。在一些实施例中,R^{WA}及R^{WB}或R^{WB}及R^{WC}与其间插原子一起形成4至7元部分不饱和碳环。在一些实施例中,R^{WA}及一个R^{L}实例与其间插原子一起形成具有0至1个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环。在一些实施例中,R^{WC}及一个R^{L}实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和环。在一些实施例中,R^{WC}及一个R^{L}实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的5至6元部分不饱和环。在一些实施例中,R^{WA}、R^{WB}及R^{WC}中的每一者是选自表1的化合物中所描绘的基团。

[0283] 如上文一般所定义,R^{WD}是卤素或$-OS(O)_2R$。在一些实施例中,R^{WD}是卤素。在一些实施例中,R^{WD}为氯或溴。在一些实施例中,R^{WD}为氯。在一些实施例中,R^{WD}为$-OS(O)_2R$。在一些实施例中,R^{WD}为$-OS(O)_2-$(任选地经取代的C_{1-3}烷基)。在一些实施例中,R^{WD}为$-OS(O)_2CH_3$或$-OS(O)_2CF_3$。在一些实施例中,R^{WD}为$-OS(O)_2-$(任选地经取代的苯基)。在一些实施例中,R^{WD}是选自表1的化合物中所描绘的基团。

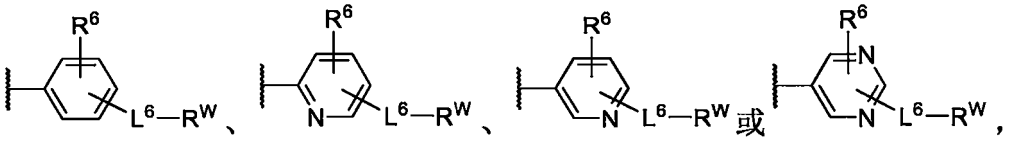
[0284] 在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:

[0285] 

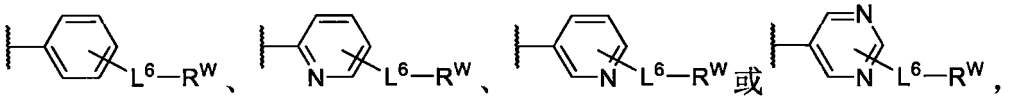
[0286] 其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:

[0287] 

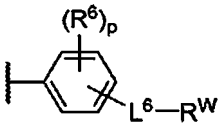
[0288] 其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:

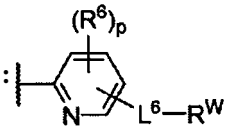
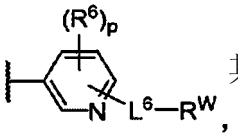
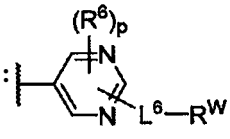
[0289] 

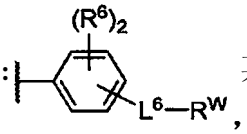
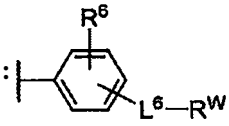
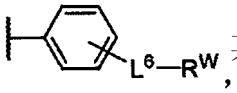
[0290] 其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:

[0291] 

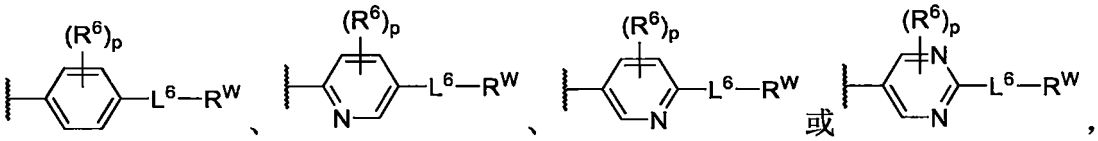
[0292] 其中L^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。

[0293] 在一些实施例中,$-Cy^6-L^6-R^W$结合在一起是:  ,其中L^6、R^6、R^W及p中的每一者如本文的实施例及各类别及子类中所定义。在一些实施例中,$-Cy^6-L^6-R^W$结合在一起

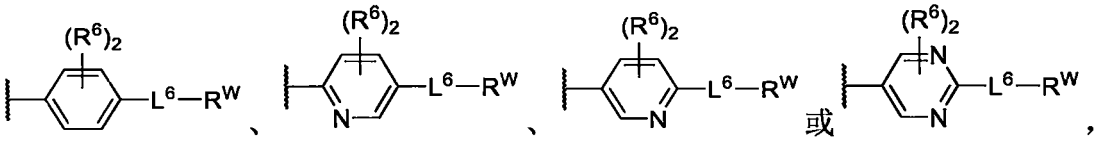
是：  ，其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中，-Cy^6-L^6-R^W结合在一起是：  ，其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中，-Cy^6-L^6-R^W结合在一起是：  ，其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。

[0294] 在一些实施例中，-Cy^6-L^6-R^W结合在一起是：  ，其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中，-Cy^6-L^6-R^W结合在一起是：  ，其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中，-Cy^6-L^6-R^W结合在一起是：  ，其中L^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。

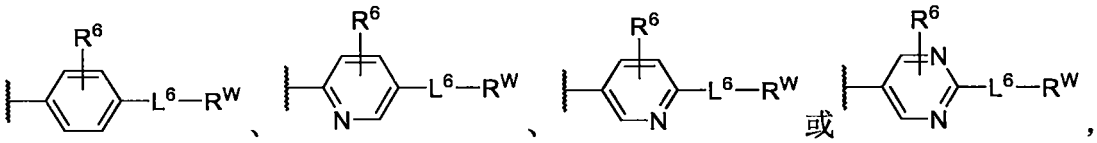
[0295] 在一些实施例中，-Cy^6-L^6-R^W结合在一起是：

[0296] 

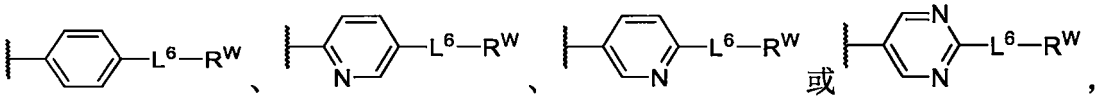
[0297] 其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中，-Cy^6-L^6-R^W结合在一起是：

[0298] 

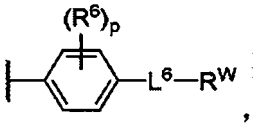
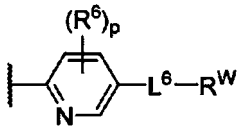
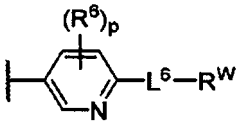
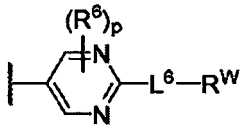
[0299] 其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中，-Cy^6-L^6-R^W结合在一起是：

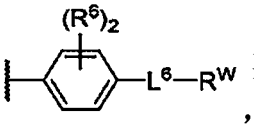
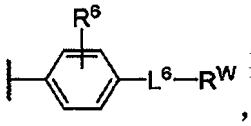
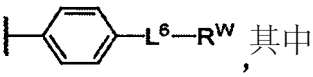
[0300] 

[0301] 其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中，-Cy^6-L^6-R^W结合在一起是：

[0302] 

[0303] 其中L^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。

[0304] 在一些实施例中,-Cy^6-L^6-R^W结合在一起是:  ,其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,-Cy^6-L^6-R^W结合在一起是:  ,其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,-Cy^6-L^6-R^W结合在一起是:  ,其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,-Cy^6-L^6-R^W结合在一起是:  ,其中L^6、R^6、R^W及p中的每一者如本文的实施例以及各类别及子类中所定义。

[0305] 在一些实施例中,-Cy^6-L^6-R^W结合在一起是:  ,其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,-Cy^6-L^6-R^W结合在一起是:  ,其中L^6、R^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。在一些实施例中,-Cy^6-L^6-R^W结合在一起是:  ,其中L^6及R^W中的每一者如本文的实施例以及各类别及子类中所定义。

[0306] 在一些实施例中,-Cy^6-L^6-R^W是选自表1的化合物中所描绘的基团。

[0307] 如上文一般所定义,R^7是H或R^B,其中R^7经t个R^{7A}实例取代。在一些实施例中,R^7是H。在一些实施例中,R^7是R^B,其中R^7经t个R^{7A}实例取代。在一些实施例中,R^7是C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;3至7元饱和或部分不饱和碳环;或具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;其中的每一者经t个R^{7A}实例取代。在一些实施例中,R^7是C_{1-6}脂肪族;3至7元饱和或部分不饱和碳环;或具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;其中的每一者经t个R^{7A}实例取代。

[0308] 在一些实施例中,R^7是C_{1-6}烷基;3至7元饱和碳环;或具有1至2个独立地选自氮及氧的杂原子的3至7元饱和单环杂环;其中的每一者经0至1个R^{7A}实例及0至3个卤素取代。在一些实施例中,R^7是经0至1个R^{7A}实例及0至3个卤素取代的C_{1-6}烷基。在一些实施例中,R^7是-

C_{1-4}烷基、-(C_{1-4}烷基)-OH、-(C_{1-4}烷基)-O-(C_{1-4}烷基),或-(C_{1-4}烷基)-N(C_{1-4}烷基)$_2$;其中各C_{1-4}烷基任选地经1、2或3个氟取代。在一些实施例中,R^7是任选地经1、2或3个氟取代的-C_{1-4}烷基。在一些实施例中,R^7是-CH_3。在一些实施例中,R^7是经0至1个R^B实例及0至3个卤素取代的C_{1-6}烷基。

[0309] 在一些实施例中,R^7是经0至1个R^{7A}实例及0至3个卤素取代的3至7元饱和碳环。在一些实施例中,R^7是具有1至2个独立地选自氮及氧的杂原子的3至7元饱和单环杂环;其经0至1个R^{7A}实例及0至3个卤素取代。在一些实施例中,R^7是具有1个氧原子的5至6元饱和单环杂环;其经0至1个R^{7A}实例及0至3个卤素取代。在一些实施例中,R^7是具有1个氧原子的5至6元饱和单环杂环;其经0至3个卤素及0至1个选自-C_{1-4}烷基、-OH、-O-(C_{1-4}烷基)或N(C_{1-4}烷基)$_2$的基团取代;其中各C_{1-4}烷基任选地经1、2或3个氟取代。在一些实施例中,R^7是具有1个氧原子的5至6元饱和单环杂环。在一些实施例中,R^7是选自表1的化合物中所描绘的基团。

[0310] 如上文一般所定义,m是0、1、2、3或4。在一些实施例中,m是0。在一些实施例中,m是1。在一些实施例中,m是2。在一些实施例中,m是3。在一些实施例中,m是4。在一些实施例中,m是0或1。在一些实施例中,m是0、1或2。在一些实施例中,m是0、1、2或3。在一些实施例中,m是1或2。在一些实施例中,m是1、2或3。在一些实施例中,m是1、2、3或4。在一些实施例中,m是2或3。在一些实施例中,m是2、3或4。在一些实施例中,m是3或4。在一些实施例中,m是选自表1中的化合物所示的值。

[0311] 如上文一般所定义,n是0、1、2、3或4。在一些实施例中,n是0。在一些实施例中,n是1。在一些实施例中,n是2。在一些实施例中,n是3。在一些实施例中,n是4。在一些实施例中,n是0或1。在一些实施例中,n是0、1或2。在一些实施例中,n是0、1、2或3。在一些实施例中,n是1或2。在一些实施例中,n是1、2或3。在一些实施例中,n是1、2、3或4。在一些实施例中,n是2或3。在一些实施例中,n是2、3或4。在一些实施例中,n是3或4。在一些实施例中,n是选自表1中的化合物所示的值。

[0312] 如上文一般所定义,p是0、1、2、3或4。在一些实施例中,p是0。在一些实施例中,p是1。在一些实施例中,p是2。在一些实施例中,p是3。在一些实施例中,p是4。在一些实施例中,p是0或1。在一些实施例中,p是0、1或2。在一些实施例中,p是0、1、2或3。在一些实施例中,p是1或2。在一些实施例中,p是1、2或3。在一些实施例中,p是1、2、3或4。在一些实施例中,p是2或3。在一些实施例中,p是2、3或4。在一些实施例中,p是3或4。在一些实施例中,p是选自表1中的化合物所示的值。

[0313] 如上文一般所定义,q是0、1、2、3或4。在一些实施例中,q是0。在一些实施例中,q是1。在一些实施例中,q是2。在一些实施例中,q是3。在一些实施例中,q是4。在一些实施例中,q是0或1。在一些实施例中,q是0、1或2。在一些实施例中,q是0、1、2或3。在一些实施例中,q是1或2。在一些实施例中,q是1、2或3。在一些实施例中,q是1、2、3或4。在一些实施例中,q是2或3。在一些实施例中,q是2、3或4。在一些实施例中,q是3或4。在一些实施例中,q是选自表1中的化合物所示的值。

[0314] 如上文一般所定义,r是0、1、2、3或4。在一些实施例中,r是0。在一些实施例中,r是1。在一些实施例中,r是2。在一些实施例中,r是3。在一些实施例中,r是4。在一些实施例中,r是0或1。在一些实施例中,r是0、1或2。在一些实施例中,r是0、1、2或3。在一些实施例中,r是1或2。在一些实施例中,r是1、2或3。在一些实施例中,r是1、2、3或4。在一些实施例中,r是

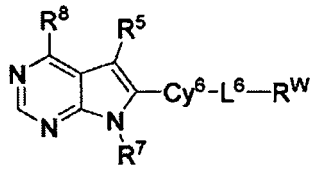
2或3。在一些实施例中,r是2、3或4。在一些实施例中,r是3或4。在一些实施例中,r是选自表1中的化合物所示的值。

[0315] 如上文一般所定义,t是0、1、2、3或4。在一些实施例中,t是0。在一些实施例中,t是1。在一些实施例中,t是2。在一些实施例中,t是3。在一些实施例中,t是4。在一些实施例中,t是0或1。在一些实施例中,t是0、1或2。在一些实施例中,t是0、1、2或3。在一些实施例中,t是1或2。在一些实施例中,t是1、2或3。在一些实施例中,t是1、2、3或4。在一些实施例中,t是2或3。在一些实施例中,t是2、3或4。在一些实施例中,t是3或4。在一些实施例中,t是选自表1中的化合物所示的值。

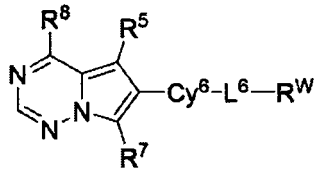
[0316] 如上文一般所定义,u是0、1、2、3或4。在一些实施例中,u是0。在一些实施例中,u是1。在一些实施例中,u是2。在一些实施例中,u是3。在一些实施例中,u是4。在一些实施例中,u是0或1。在一些实施例中,u是0、1或2。在一些实施例中,u是0、1、2或3。在一些实施例中,u是1或2。在一些实施例中,u是1、2或3。在一些实施例中,u是1、2、3或4。在一些实施例中,u是2或3。在一些实施例中,u是2、3或4。在一些实施例中,u是3或4。在一些实施例中,u是选自表1中的化合物所示的值。

[0317] 在一些实施例中,本发明提供式I-1化合物,包含吡咯并嘧啶、吡咯并三嗪、吡唑并吡嗪、吡咯并吡啶、呋喃并嘧啶、噻吩并嘧啶或吡咯并哒嗪酮,从而形成式Ia、Ib、Ic、Id、Ie、If、Ig或Ih化合物:

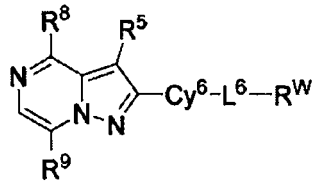
[0318]



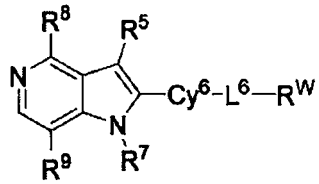
Ia



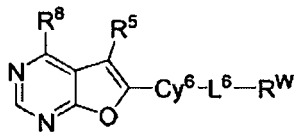
Ib



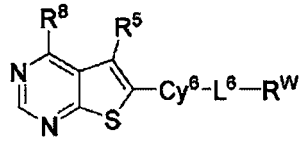
Ic



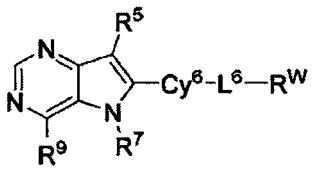
Id



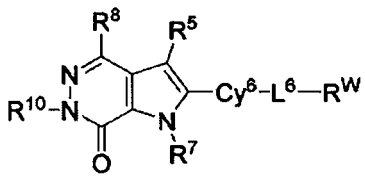
Ie



If



Ig

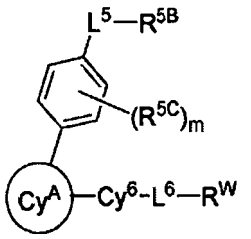


Ih

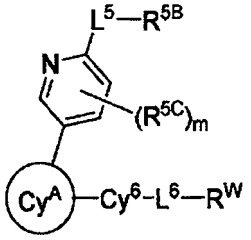
[0319] 或其药学上可接受的盐,其中Cy^6、L^6、R^W、R^5、R^7、R^8、R^9及R^{10}中的每一者如本文的实

施例以及各类别及子类中所定义。

[0320] 在一些实施例中,本发明提供式I-1化合物,其中R^{5A}是亚苯基、亚吡啶基或亚环己烯基,从而形成式II-1、III-1、IV-1或V-1化合物:

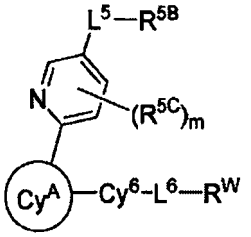


II-1

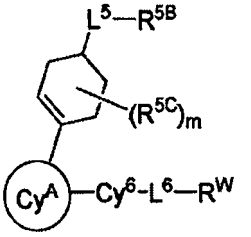


III-1

[0321]



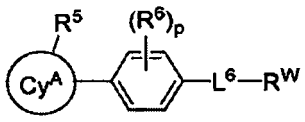
IV-1



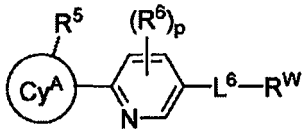
V-1

[0322] 或其药学上可接受的盐,其中Cy^A、Cy^6、L^5、L^6、R^{5B}、R^{5C}、R^W及m中的每一者如本文的实施例及各类别及子类中所定义。

[0323] 在一些实施例中,本发明提供式I-1化合物,其中Cy^6是亚苯基、亚吡啶基或亚嘧啶基,从而形成式VI-1、VII-1、VIII-1或IX-1化合物:

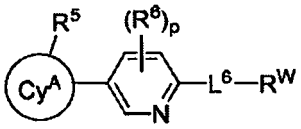


VI-1

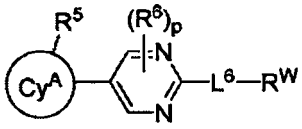


VII-1

[0324]



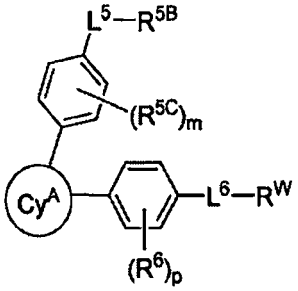
VIII-1



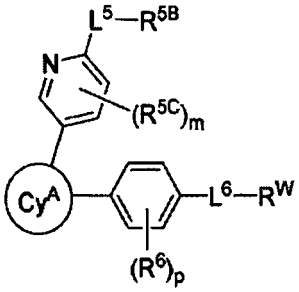
IX-1

[0325] 或其药学上可接受的盐,其中Cy^A、L^6、R^5、R^W、R^6及p中的每一者如本文的实施例及各类别及子类中所定义。

[0326] 在一些实施例中,本发明提供式II-1、III-1、IV-1或V-1化合物,其中Cy^6是亚苯基,从而分别形成式X-1、XI-1、XII-1或XIII-1化合物:

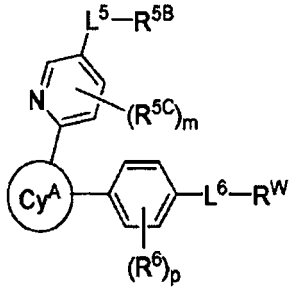


X-1

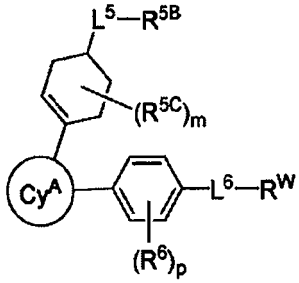


XI-1

[0327]



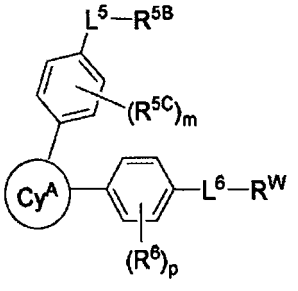
XII-1



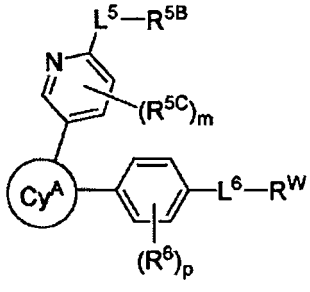
XIII-1

[0328] 或其药学上可接受的盐,其中Cy^A、L^5、L^6、R^{5B}、R^{5C}、R^W、R^6、m及p中的每一者如本文的实施例及各类别及子类中所定义。

[0329] 举例来说,在一些实施例中,本发明提供式X-1、XI-1、XII-1或XIII-1化合物:

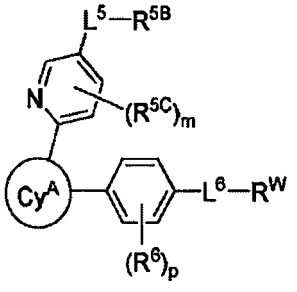


X-1

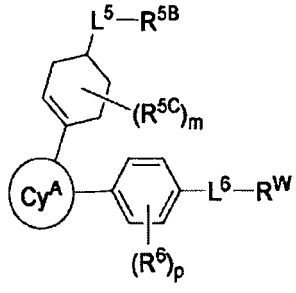


XI-1

[0330]

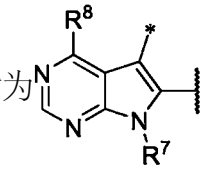
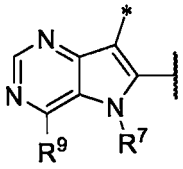
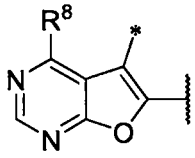
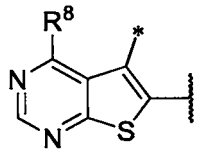
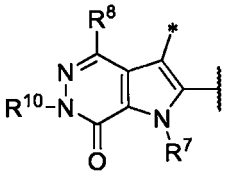


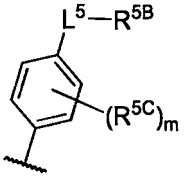
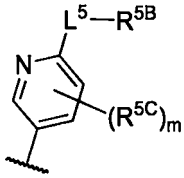
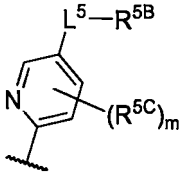
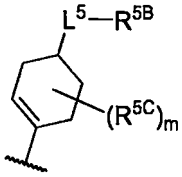
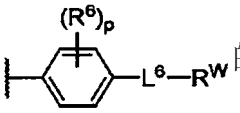
XII-1



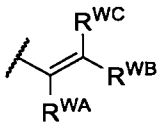
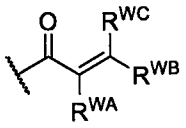
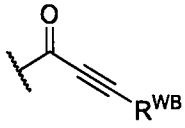
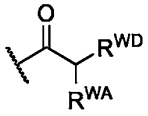
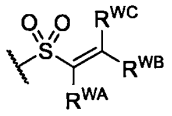
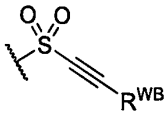
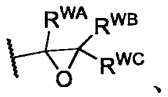
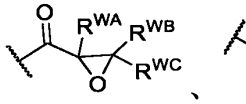
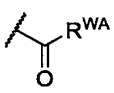
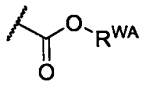
XIII-1

[0331] 或其药学上可接受的盐,其中:

[0332] Cy^A为  、 、 、 、  、  、  或  ，

[0333] 其中所述Cy^A中的*表示连至以下的键结：  、  、  或  ，并且Cy^A中的 表示连至  的键结；

[0334] R^{5B}是氢或R^B，其中R^{5B}经n个R^{5D}实例取代；

[0335] R^W是卤素、-CN、  、、  、  、  、  、  、  、  、  或  ；

[0336] R^6的各实例独立地是R^A或R^B，其中R^6经q个R^C实例取代；或

[0337] 两个R^6实例，或一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环；其中所述环经r个R^C实例取代；

[0338] R^7是H或R^B，其中R^7经t个R^{7A}实例取代；

[0339] R^8是H、$-NR_2$、卤素、-OH，或任选地经1至3个卤素取代的C_{1-6}脂肪族；

[0340] R^6是H、$-NR_2$、卤素，或任选地经1至3个卤素取代的C_{1-6}脂肪族；

[0341] R^{10}是H或任选地经1至3个卤素取代的C_{1-6}脂肪族；

[0342] L^5及L^6中的每一者独立地是共价键，或C_{1-4}饱和或不饱和、直链或分支链二价烃链，其中所述链的一或两个亚甲基单元任选地且独立地经以下置换：$-CH(R^L)-$、$-C(R^L)_2-$、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、$-N(R^L)-$、-NHC(O)-、$-N(R^L)C(O)-$、-C(O)NH-、$-C(O)N(R^L)-$、$-NHS(O)_2-$、$-N(R^L)S(O)_2-$、$-S(O)_2NH-$、$-S(O)_2N(R^L)-$、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或$-S(O)_2-$；

[0343] R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;或

[0344] R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例,或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环;

[0345] R^{WD}是卤素或-OS(O)$_2$R;

[0346] R^{5C}、R^{5D}、R^{7A}及R^L的各实例独立地是R^A或R^B,且经u个R^C实例取代;

[0347] R^A的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$或-N(R)S(O)$_2$R;

[0348] R^B的各实例独立地是C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;或具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环;

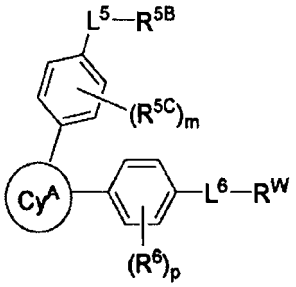
[0349] R^C的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-S(O)$_2$F、-OS(O)$_2$F、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R,或选自以下的任选地经取代的基团:$C_{1-6}$脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;

[0350] 各R独立地是氢或选自以下的任选地经取代的基团:C_{1-6}脂肪族;苯基;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环;及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环,或:

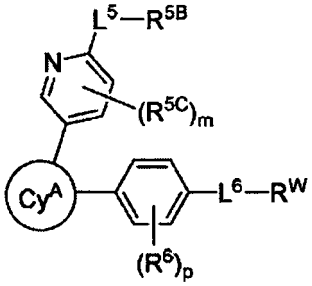
[0351] 同一氮上的两个R基团与其间插原子一起形成4至7元饱和、部分不饱和或杂芳基环,除所述氮之外,所述环还具有0至3个独立地选自氮、氧及硫的杂原子;及

[0352] m、n、p、q、r、t及u中的每一者独立地是0、1、2、3或4。

[0353] 在一些实施例中,本发明提供式X-1、XI-1、XII-1或XIII-1化合物:

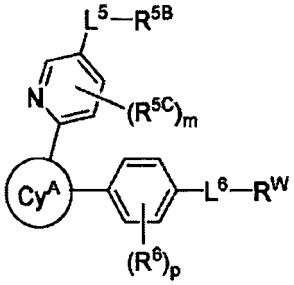


X-1

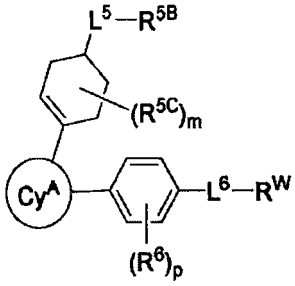


XI-1

[0354]

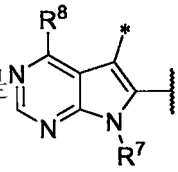
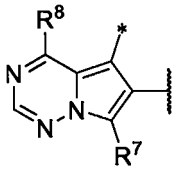
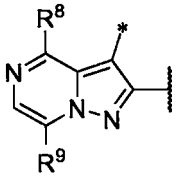
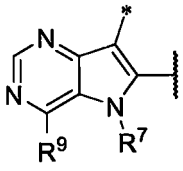
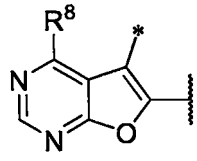
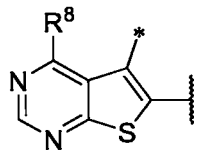
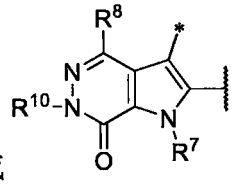


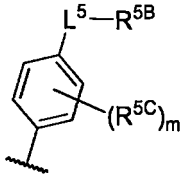
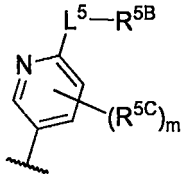
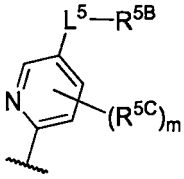
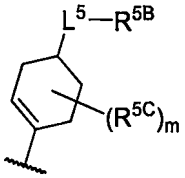
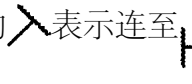
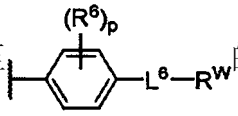
XII-1



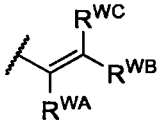
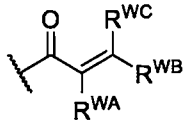
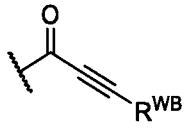
XIII-1

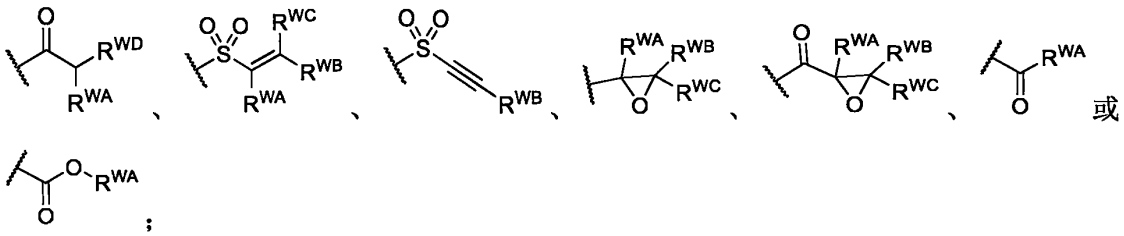
[0355] 或其药学上可接受的盐,其中:

[0356] Cy^A是  、  、  、 、  、  、  或  ,

[0357] 其中Cy^A中的*表示连至以下的键结:  、  、  、  且Cy^A中的  表示连至  的键结;或,

[0358] R^{5B}的氢或R^B,其中R^{5B}经n个R^{5D}实例取代;

[0359] R^W是卤素、-CN、  、、  、  、



[0360] R^6的各实例独立地是R^A或R^B,其中R^6经q个R^C实例取代;或

[0361] 两个R^6实例,或一个R^6实例及一个R^L实例与其间插原子一起形成具有0至4个独立地选自氮、氧及硫的杂原子的4至7元部分不饱和或芳香族环;其中所述环经r个R^C实例取代;

[0362] R^7是H或R^B,其中R^7经t个R^{7A}实例取代;

[0363] R^8是H、-NR_2、卤素、-OH,或任选地经1至3个卤素取代的C_{1-6}脂肪族;

[0364] R^6是H、-NR_2、卤素,或任选地经1至3个卤素取代的C_{1-6}脂肪族;

[0365] R^{10}是H或任选地经1至3个卤素取代的C_{1-6}脂肪族;

[0366] L^5及L^6中的每一者独立地是共价键,或C_{1-4}饱和或不饱和、直链或分支链二价烃链,其中所述链的一或两个亚甲基单元任选地且独立地经以下置换:-CH(R^L)-、-C(R^L)$_2$-、C_{3-5}亚环烷基、3至5元亚杂环烷基、5至6元亚杂芳基、-NH-、-N(R^L)-、-NHC(O)-、-N(R^L)C(O)-、-C(O)NH-、-C(O)N(R^L)-、-NHS(O)$_2$-、-N(R^L)S(O)$_2$-、-S(O)$_2$NH-、-S(O)$_2$N(R^L)-、-O-、-C(O)-、-OC(O)-、-C(O)O-、-S-、-S(O)-或-S(O)$_2$-;

[0367] R^{WA}、R^{WB}及R^{WC}中的每一者独立地是氢、氘、卤素、-CN、-C(O)R、-C(O)OR、-C(O)NR_2、-C(O)N(R)OR,或选自以下的任选地经取代的基团:C_{1-6}脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环;或

[0368] R^{WA}及R^{WB}、R^{WB}及R^{WC}、R^{WA}及一个R^L实例,或R^{WC}及一个R^L实例与其间插原子一起形成具有0至2个独立地选自氮、氧及硫的杂原子的4至7元饱和或部分不饱和环;

[0369] R^{WD}是卤素或-OS(O)$_2$R;

[0370] R^{5C}、R^{5D}、R^{7A}及R^L的各实例独立地是R^A或R^B,且经u个R^C实例取代;

[0371] R^A的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$或-N(R)S(O)$_2$R;

[0372] R^B的各实例独立地是C_{1-6}脂肪族;苯基;具有1至4个独立地选自氮、氧及硫的杂原子的5至6元单环杂芳基环;具有1至4个独立地选自氮、氧及硫的杂原子的8至10元双环杂芳基环;3至7元饱和或部分不饱和碳环;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和单环杂环;或具有1至4个独立地选自氮、氧及硫的杂原子的7至12元饱和或部分不饱和双环杂环;

[0373] R^C的各实例独立地是侧氧基、卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-S(O)$_2$F、-OS(O)$_2$F、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R,或选自以下的任选地经取代的基团:$C_{1-6}$脂肪族、苯基、具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环,及具有1至4个独立地选自氮、氧及硫的杂

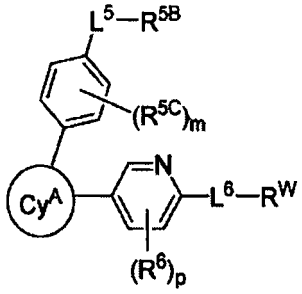
原子的5至6元杂芳基环;

[0374] 各R独立地是氢或选自以下的任选地经取代的基团:C_{1-6}脂肪族;苯基;具有1至2个独立地选自氮、氧及硫的杂原子的3至7元饱和或部分不饱和杂环;及具有1至4个独立地选自氮、氧及硫的杂原子的5至6元杂芳基环,或:

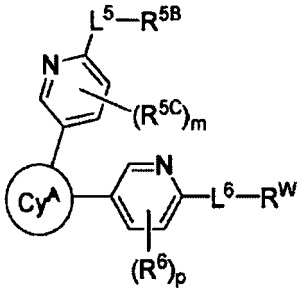
[0375] 同一氮上的两个R基团与其间插原子一起形成4至7元饱和、部分不饱和或杂芳基环,除所述氮之外,所述环还具有0至3个独立地选自氮、氧及硫的杂原子;及

[0376] m、n、p、q、r、t及u中的每一者独立地是0、1、2、3或4。

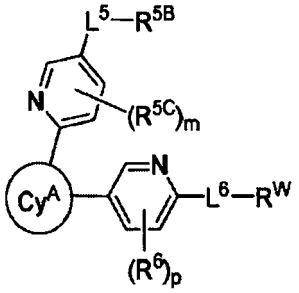
[0377] 在一些实施例中,本发明提供式II-1、III-1、IV-1或V-1化合物,其中Cy^6为亚吡啶基,从而分别形成式XIV-1、XV-I、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1或XXI-1化合物:



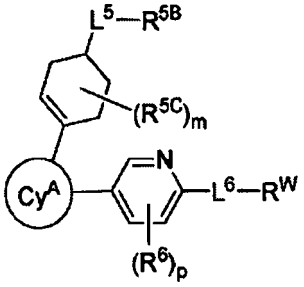
XIV-1



XV-1

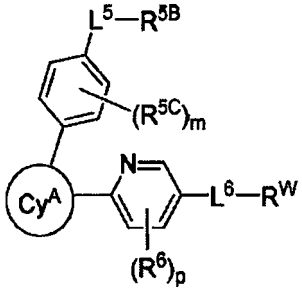


XVI-1

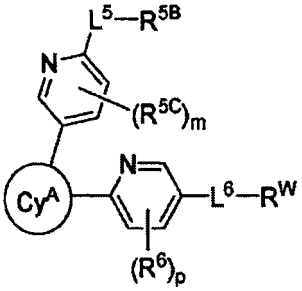


XVII-1

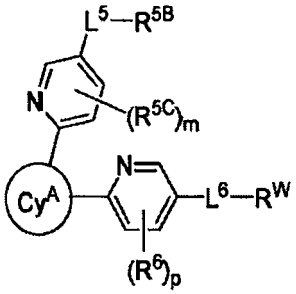
[0378]



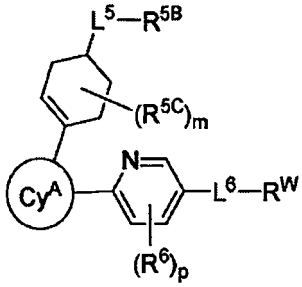
XVIII-1



XIX-1



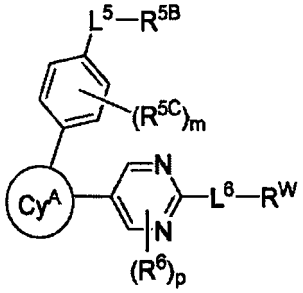
XX-1



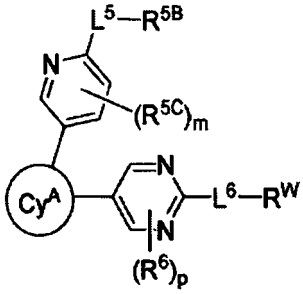
XXI-1

[0379] 或其药学上可接受的盐,其中Cy^A、L^5、L^6、R^{5B}、R^{5C}、R^W、R^6、m及p中的每一者如本文的实施例及各类别及子类中所定义。

[0380] 在一些实施例中,本发明提供式II-1、III-1、IV-1或V-1化合物,其中Cy^6是亚嘧啶基,从而分别形成式XXII-1、XXIII-1、XXIV-1或XXV-1化合物:

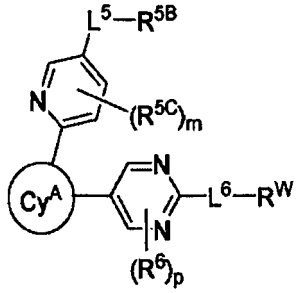


XXII-1

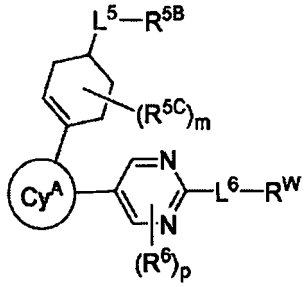


XXIII-1

[0381]

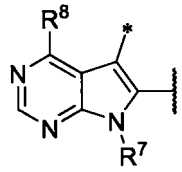
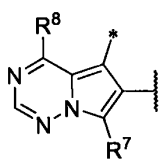
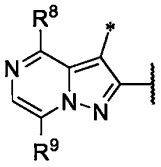
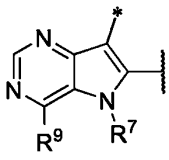
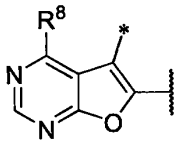
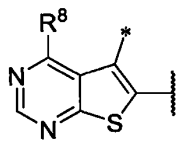
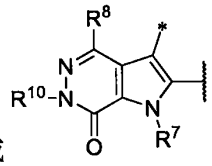


XXIV-1

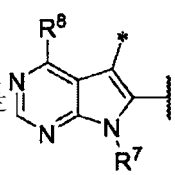


XXV-1

[0382] 或其药学上可接受的盐,其中Cy^A、L^5、L^6、R^{5B}、R^{5C}、R^W、R^6、m及p中的每一者如本文的实施例及各类别及子类中所定义。

[0383] 在一些实施例中,本发明提供式I-1、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、X11-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中Cy^A为  、  、  、 、  、  、  、  或,

[0384] 其中 表示连至的R^5的键结且表示连至Cy^6的键结。

[0385] 在一些实施例中,本发明提供式I-1、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中Cy^A是  其中表示连至R^5的键结,

且入表示连至Cy^6的键结。

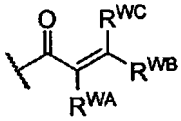
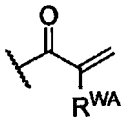
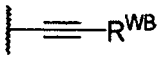
[0386] 在一些实施例中,本发明提供I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中L^5是-O-、-C(O)-、-C(O)NH-或-C(O)N(R^L)-。在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中L^5是-O-。在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中L^5是-C(O)-。在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中L^5是-C(O)NH-。在一些实施例中,本发明提供I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVVII-1、XIX_1、XX_1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中L^5是-C(O)N(R^L)-。

[0387] 在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中L^6是-NH-或-N(R^L)-。在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中L^6是-NH-。

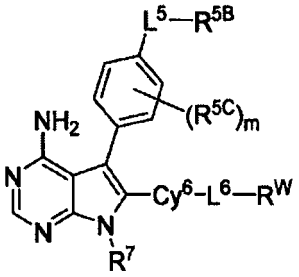
[0388] 在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中m是0或1。在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中m是0。在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII_1、XXIII_1、XXIV-1或XXV-1化合物,其中m是1。

[0389] 在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中p是0或1。在一些实施例中,本发明提供I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中p是0。在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、

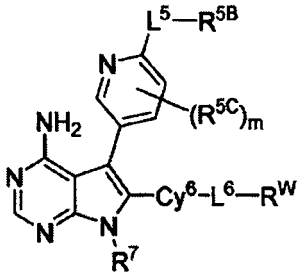
XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中p是1。

[0390] 在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中R^W是  在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中R^W是  在一些实施例中,本发明提供式I-1、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、II-1、III-1、IV-1、V-1、VI-1、VII-1、VIII-1、IX-1、X-1、XI-1、XII-1、XIII-1、XIV-1、XV-1、XVI-1、XVII-1、XVIII-1、XIX-1、XX-1、XXI-1、XXII-1、XXIII-1、XXIV-1或XXV-1化合物,其中R^W是  。

[0391] 在一些实施例中,本发明提供式I化合物,其中R^{5A}是亚苯基、亚吡啶基或亚环己烯基,从而形成式II、III、IV或V化合物:

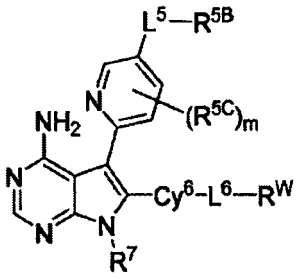


II

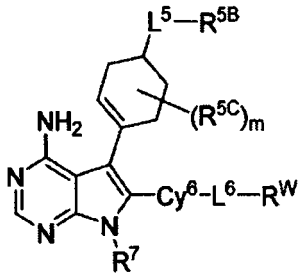


III

[0392]



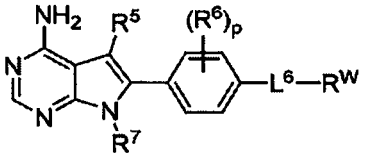
IV



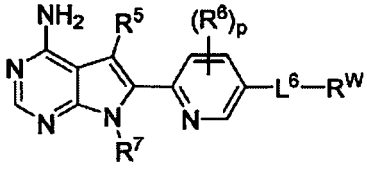
V

[0393] 或其药学上可接受的盐,其中Cy^6、L^5、L^6、R^{5B}、R^{5C}、R^W、R^7及m中的每一者如本文的实施例及各类别及亚类中所定义。

[0394] 在一些实施例中,本发明提供式I化合物,其中Cy^6是亚苯基、亚吡啶基或亚嘧啶基,从而形成式VI、VII、VIII或IX化合物:

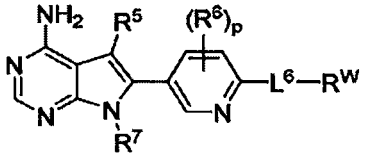


VI

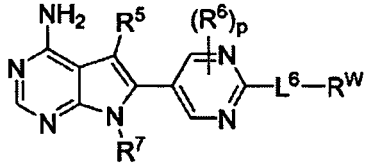


VII

[0395]



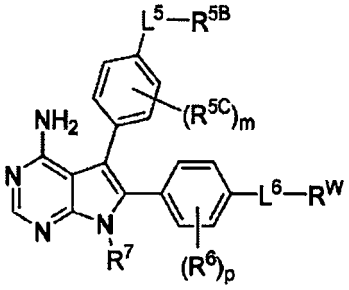
VIII



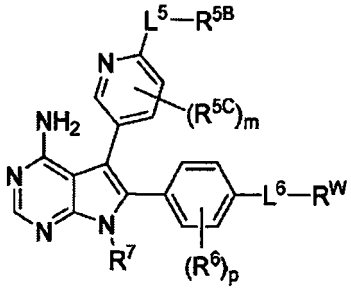
IX

[0396] 或其药学上可接受的盐,其中L^6、R^5、R^W、R^6、R^7及p中的每一者如本文的实施例及各类别及亚类中所定义。

[0397] 在一些实施例中,本发明提供式II、III、IV或V化合物,其中Cy^6是亚苯基,从而分别形成式X、XI、XII或XIII化合物:

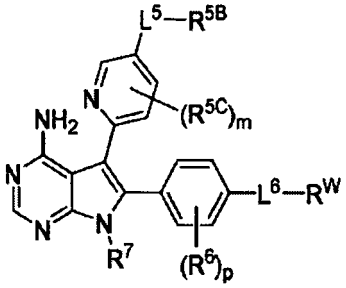


X

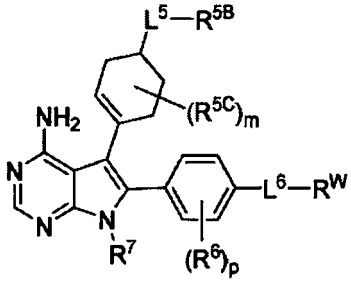


XI

[0398]



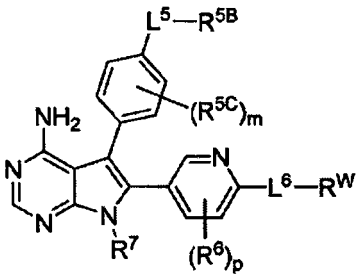
XII



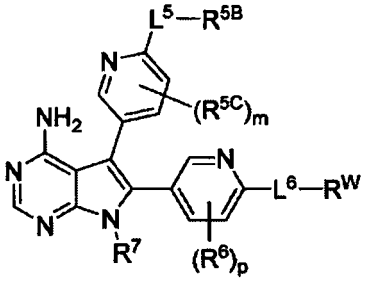
XIII

[0399] 或其药学上可接受的盐,其中L^5、L^6、R^{5B}、R^{5C}、R^W、R^6、R^7、m及p中的每一者如本文的实施例及各类别及子类中所定义。

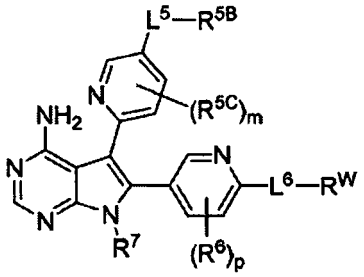
[0400] 在一些实施例中,本发明提供式II、III、IV或V化合物,其中Cy^6是亚吡啶基,从而分别形成式XIV、XV、XVI、XVII、XVIII、XIX、XX或XXI化合物:



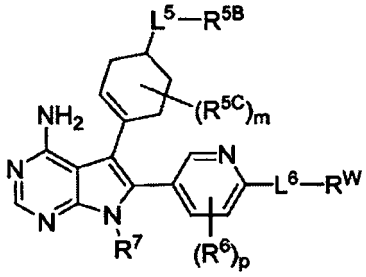
XIV



XV

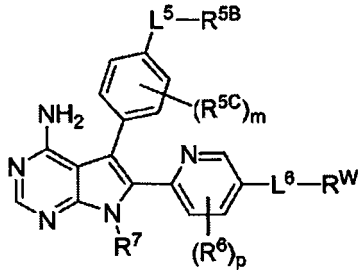


XVI

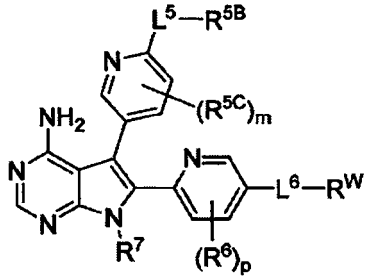


XVII

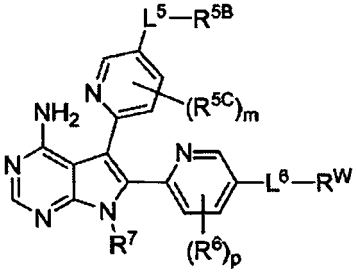
[0401]



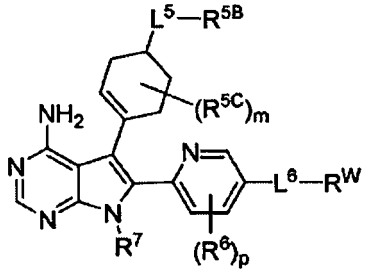
XVIII



XIX



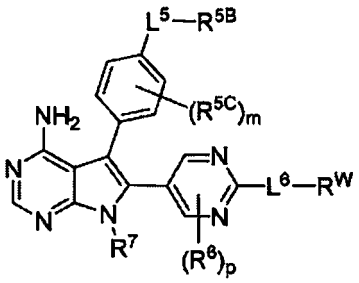
XX



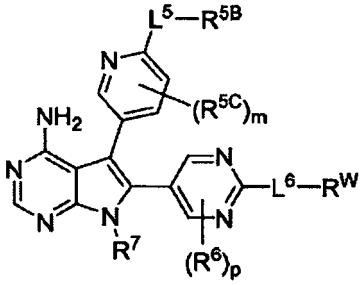
XXI

[0402] 或其药学上可接受的盐,其中Cy^A、L^5、L^6、R^{5B}、R^{5C}、R^W、R^6、m及p中的每一者如本文的实施例及各类别及子类中所定义。

[0403] 在一些实施例中,本发明提供式II、III、IV或V化合物,其中Cy^6是亚嘧啶基,从而分别形成式XXII、XXIII、XXIV或XXV化合物:

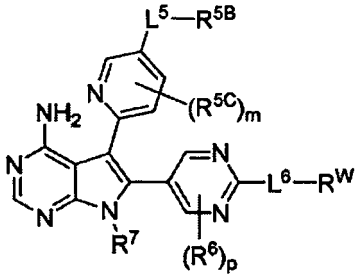


XXII

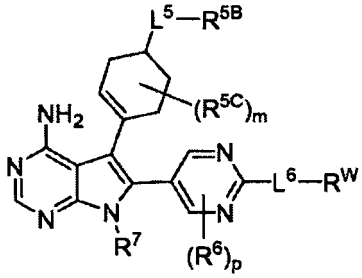


XXIII

[0404]



XXIV



XXV

[0405] 或其药学上可接受的盐,其中Cy^A、L^5、L^6、R^{5B}、R^{5C}、R^W、R^6、m及p中的每一者如本文的实施例及各类别及子类中所定义。

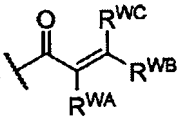
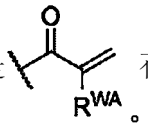
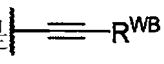
[0406] 在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中L^5是-O-、-C(O)-、-C(O)NH-或-C(O)N(R^L)-。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中L^5是-O-。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中L^5是-C(O)-。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中L^5是-C(O)NH-。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中L^5是-C(O)N(R^L)-。

[0407] 在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中L^6是-NH-或-N(R^L)-。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中L^6是-NH-。

[0408] 在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中m是0或1。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中m是0。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中m是1。

[0409] 在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中p是0或1。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中p是0。在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中p是1。

[0410] 在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或

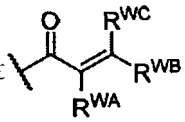
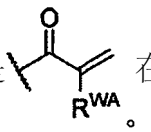
XIII化合物,其中R^W是  在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中R^W是  在一些实施例中,本发明提供式I、II、III、IV、V、VI、VII、VIII、IX、X、XI、XII或XIII化合物,其中R^W是  。

[0411] 在一些实施例中,本发明提供XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中L^5为-O-、-C(O)-、-C(O)NH-,或-C(O)N(R^L)-。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中L^5是-O-。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中L^5是-C(O)-。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中L^5是-C(O)NH-。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中L^5是-C(O)N(R^L)-。

[0412] 在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中L^6是-NH-或-N(R^L)-。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中L^6是-NH-。

[0413] 在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中m是0或1。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中m是0。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中m是1。

[0414] 在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中p是0或1。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中p是0。在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中p是1。

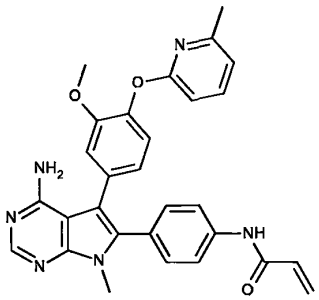
[0415] 在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中R^W是  在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中R^W是  在一些实施例中,本发明提供式XIV、XV、XVI、XVII、XVIII、XIX、XX、XXI、XXII、XXIII、XXIV或XXV化合物,其中R^W是。

[0416] 本发明的化合物的实例包括本文中的表及范例中所列的那些化合物或其药学上可接受的盐、立体异构体或立体异构体混合物。在一些实施例中,本发明包含选自下表1中所描绘的化合物的化合物或其药学上可接受的盐、立体异构体或立体异构体混合物。在一

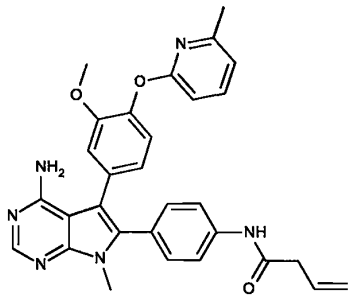
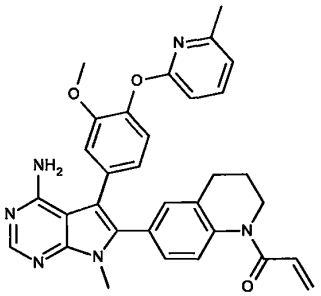
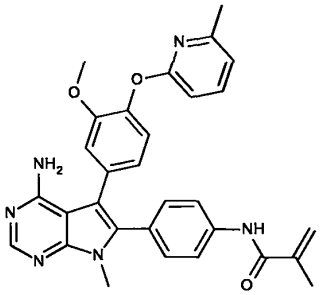
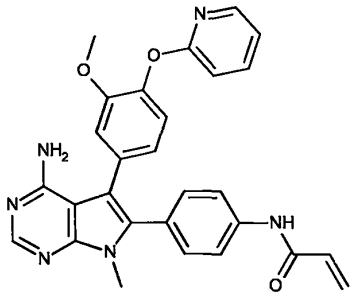
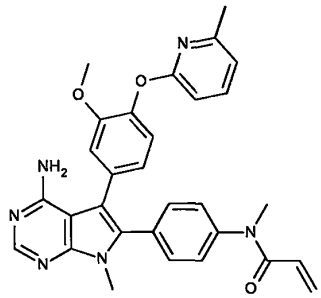
些实施例中,本发明提供下表1中所示的化合物或其药学上可接受的盐。在一些实施例中,本发明提供下表1中所示的化合物。

[0417] 表1.具有生物活性数据的本发明代表性化合物.

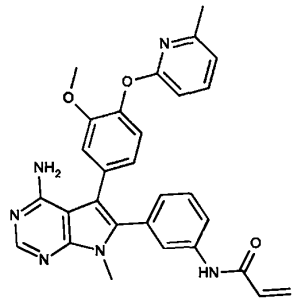
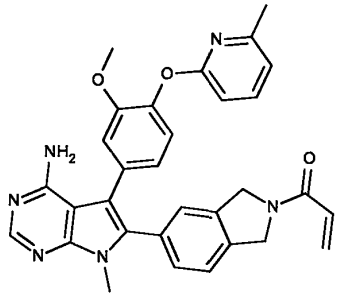
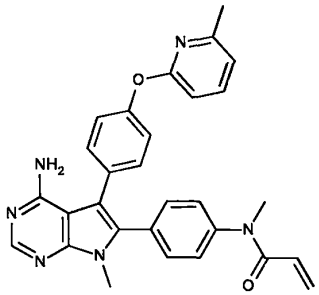
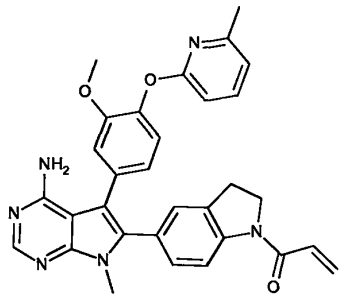
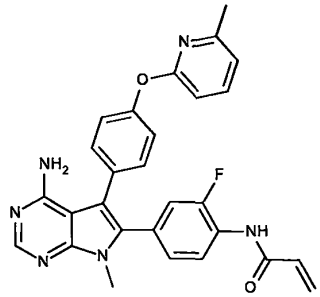
[0418]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1		A	A

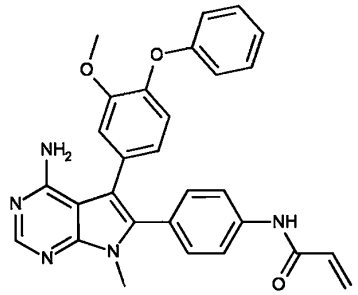
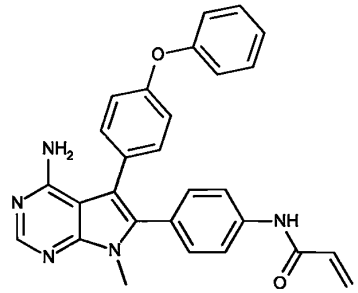
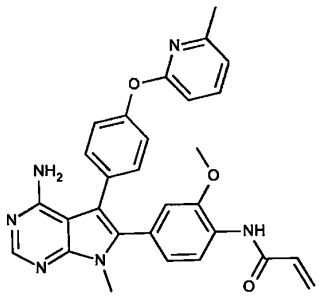
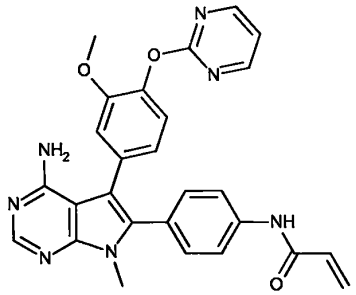
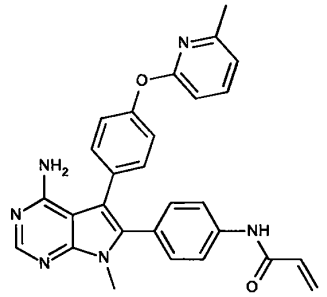
[0419]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
2		C	
3		A	
4		A	A
5		A	A
6		B	

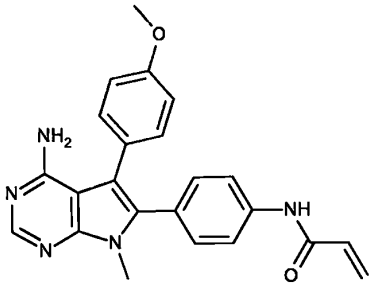
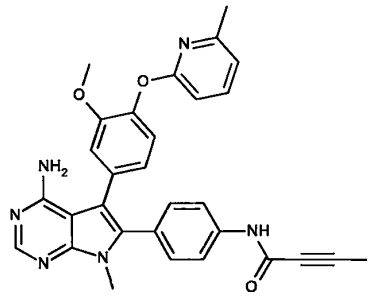
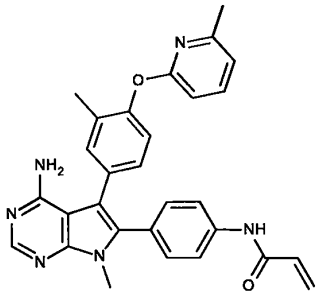
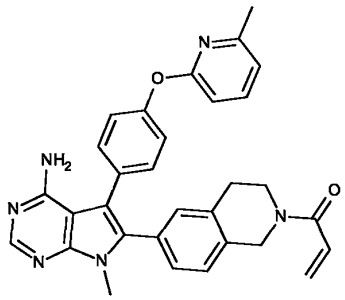
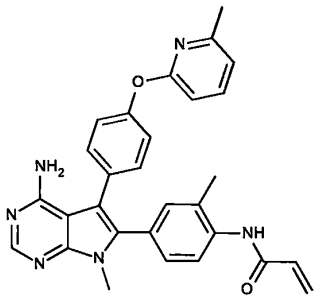
[0420]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
7		A	
8		A	
9		A	
10		A	
11		A	A

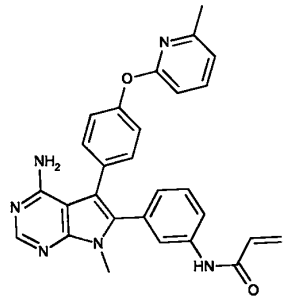
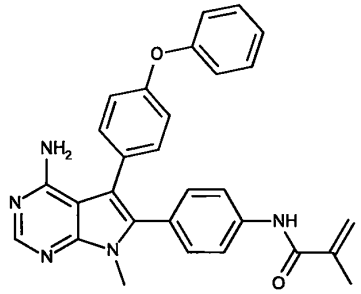
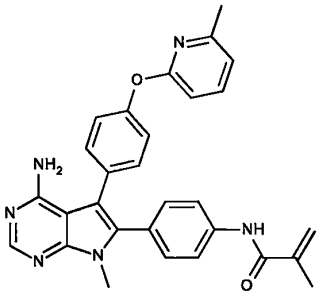
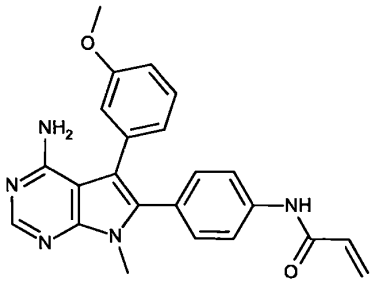
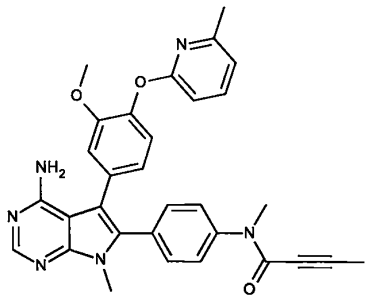
[0421]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
12		A	
13		A	
14		A	A
15		A	A
16		A	A

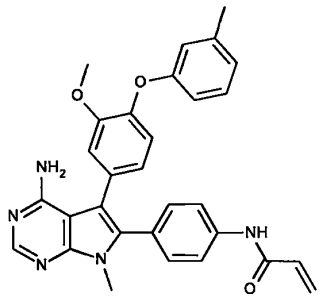
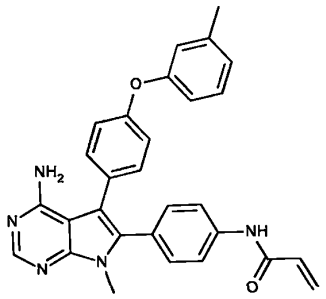
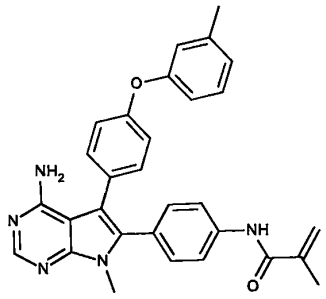
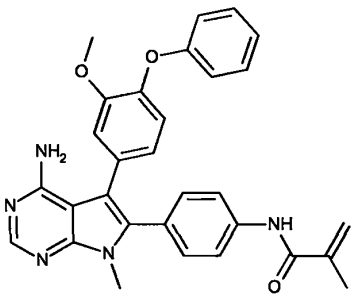
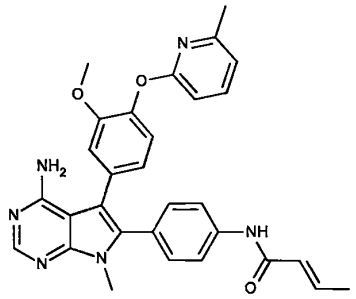
[0422]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
17		A	
18		A	A
19		A	
20		B	
21		A	

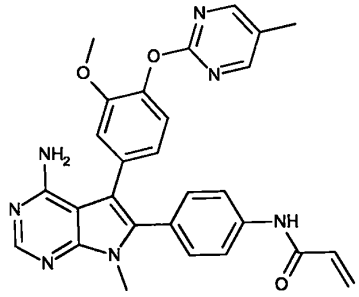
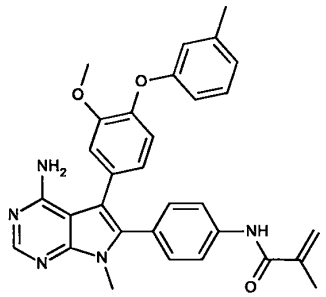
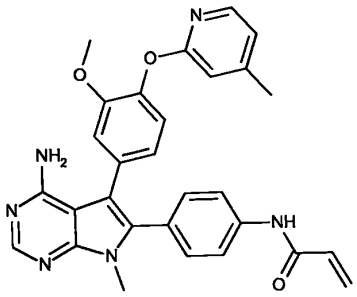
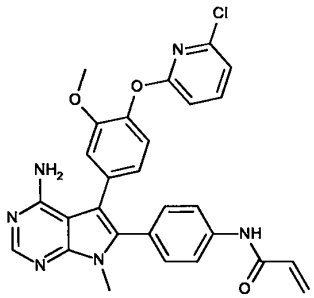
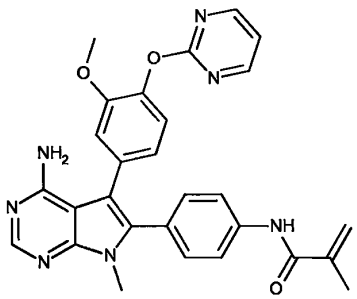
[0423]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
22		A	
23		C	
24		A	A
25		A	
26		A	

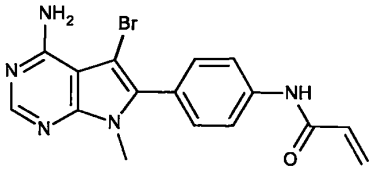
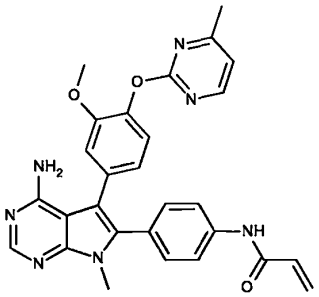
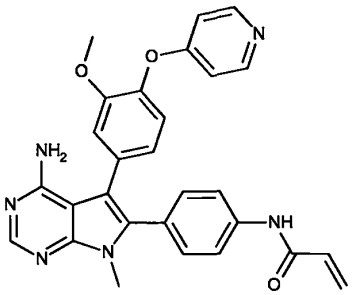
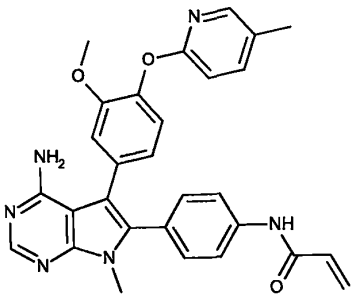
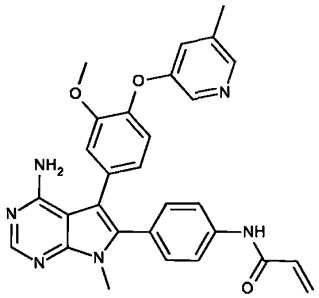
[0424]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
27		A	
28		A	
29		C	
30		C	
31		A	A

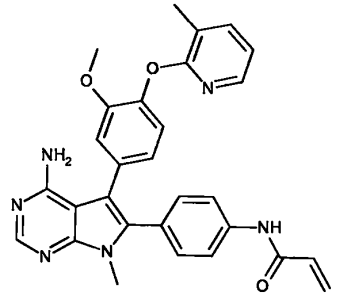
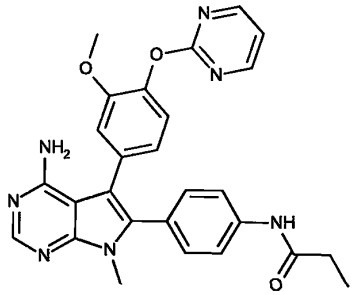
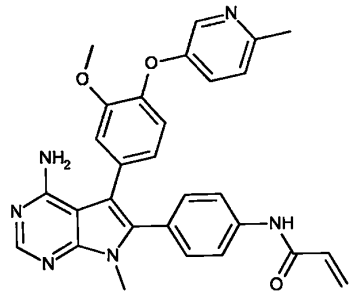
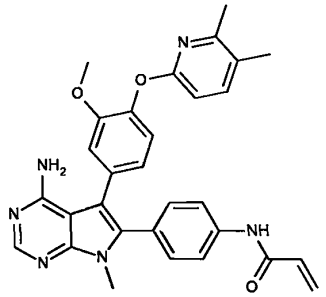
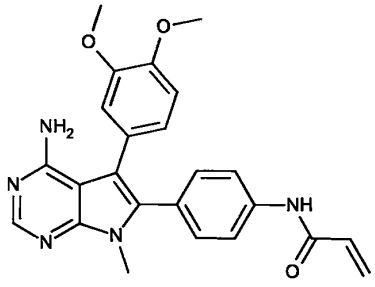
[0425]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
32		A	A
33		C	
34		A	
35		A	A
36		C	B

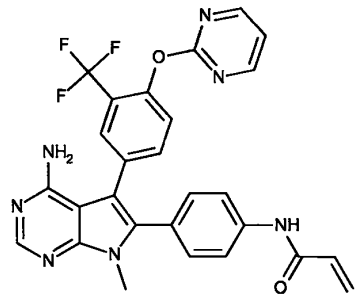
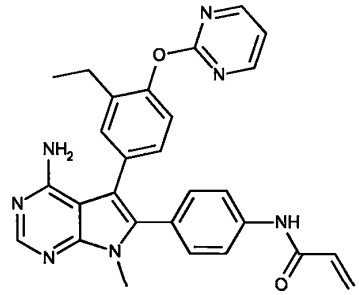
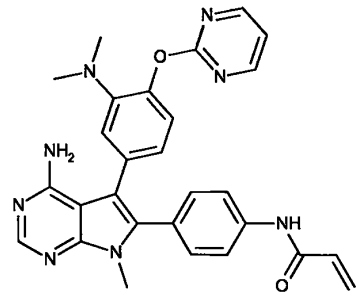
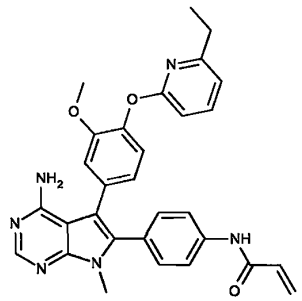
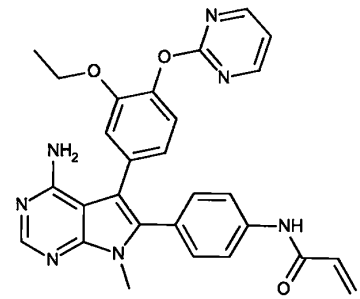
[0426]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
37		A	
38		A	A
39		B	
40		A	
41		A	

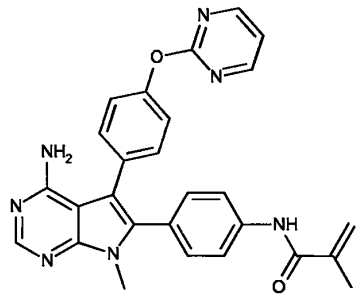
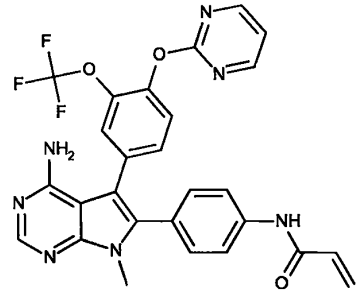
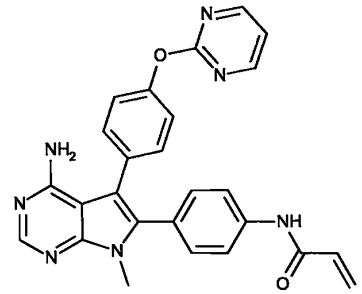
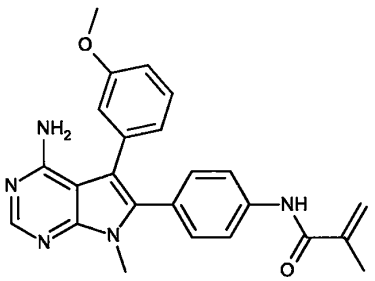
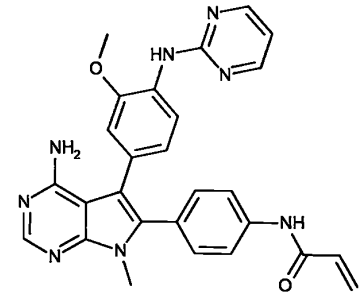
[0427]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
42		A	
43		D	
44		A	
45		A	A
46		A	

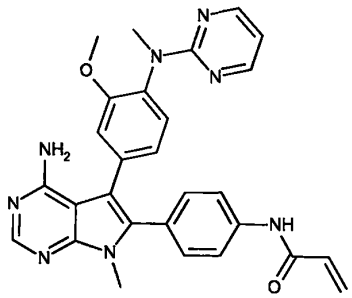
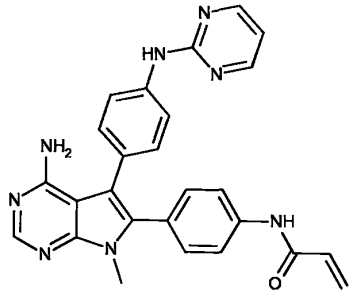
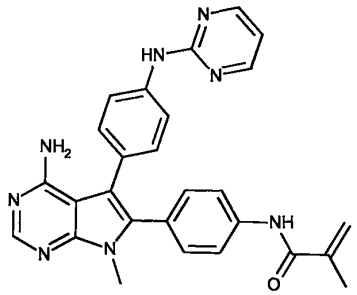
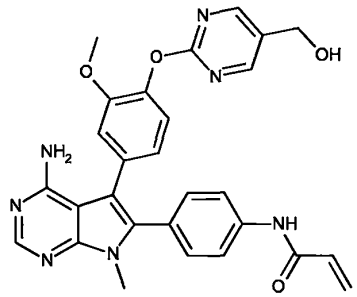
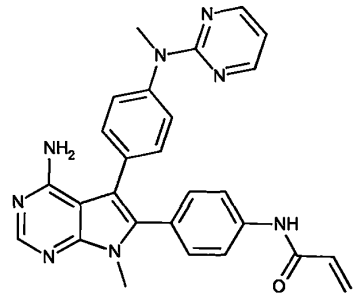
[0428]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
47		A	A
48		A	A
49		A	A
50		A	A
51		A	A

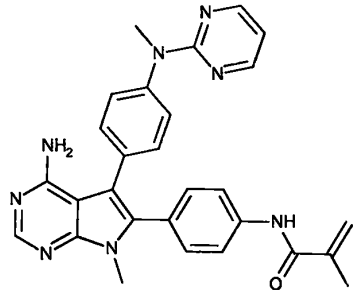
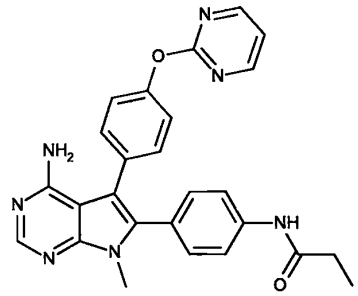
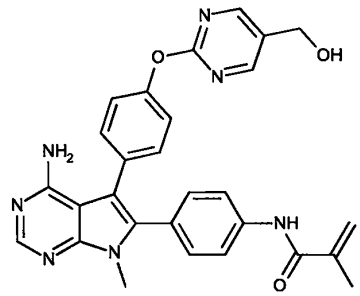
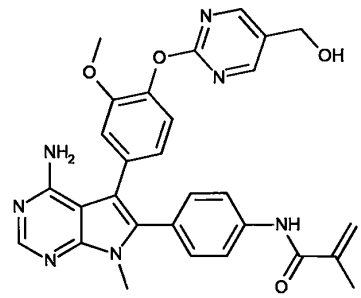
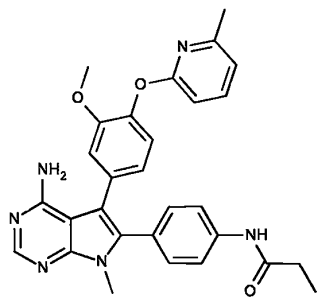
[0429]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
52		A	
53		A	A
54		A	A
55		C	
56		A	

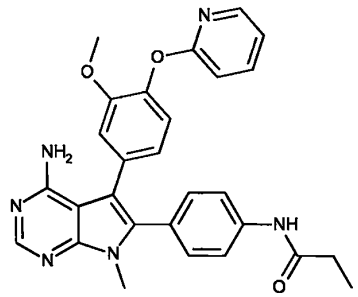
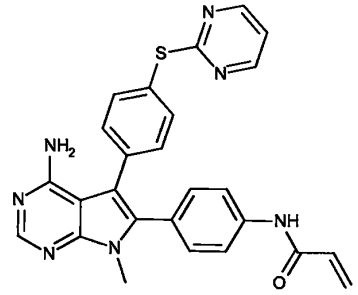
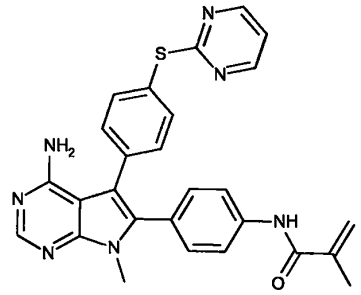
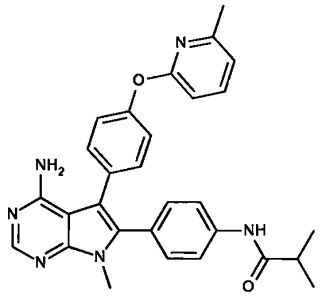
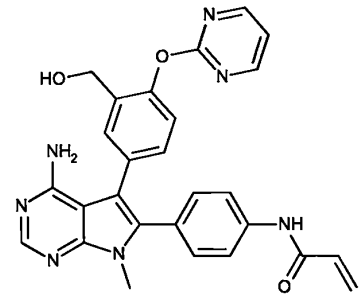
[0430]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
57		B	
58		A	
59		B	
60		A	C
61		A	

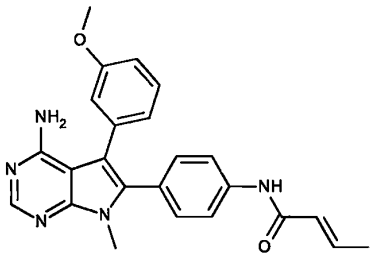
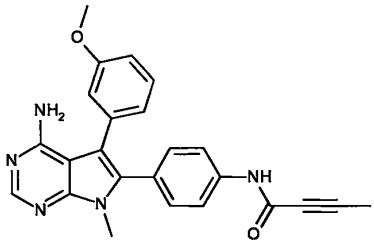
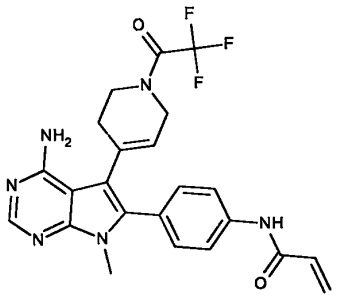
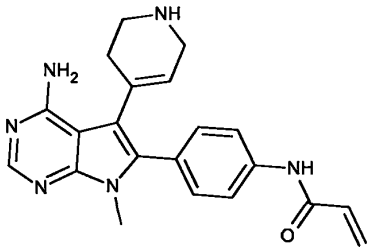
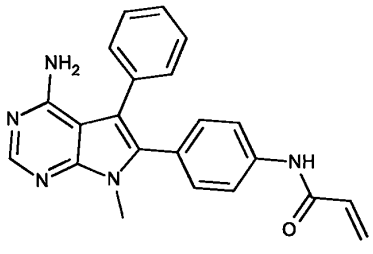
[0431]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
62		D	
63		D	
64		D	
65		D	
66		D	

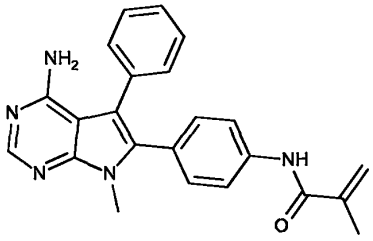
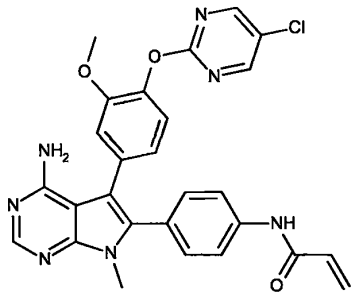
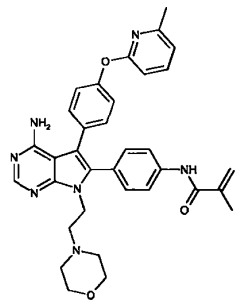
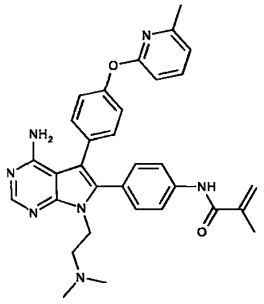
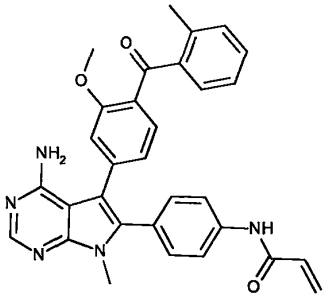
[0432]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
67		D	
68		A	
69		C	C
70		C	C
71		C	

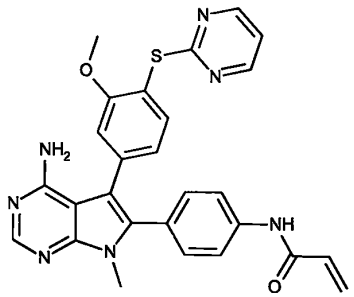
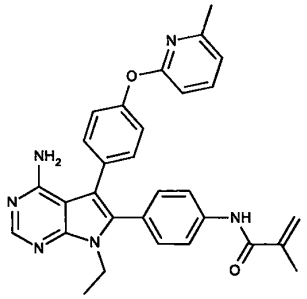
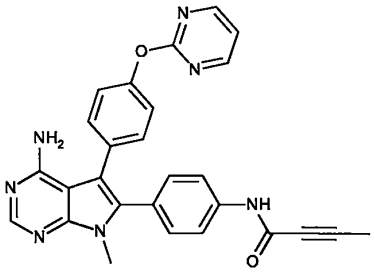
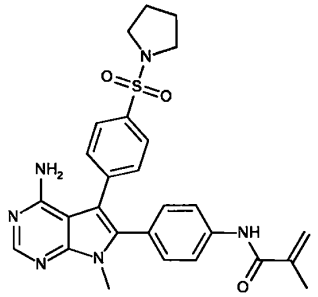
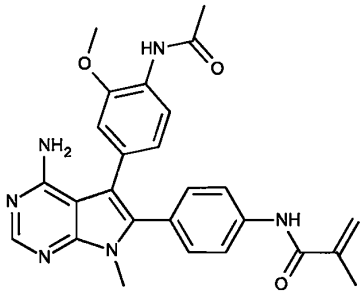
[0433]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
72		C	
73		B	
74		C	
75		C	
76		B	

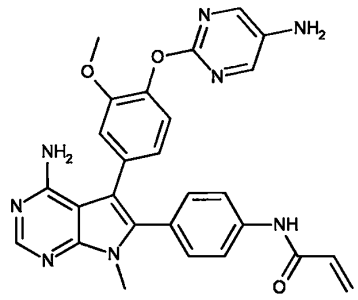
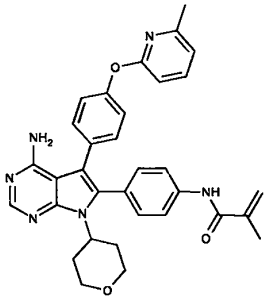
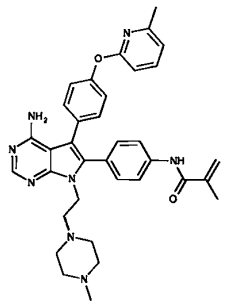
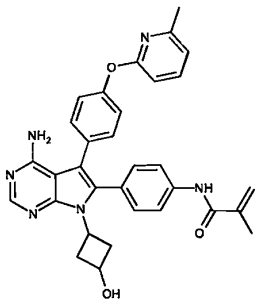
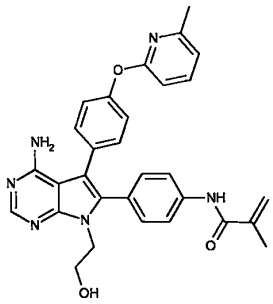
[0434]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
77			
78		A	A
79		B	
80		B	
81		A	

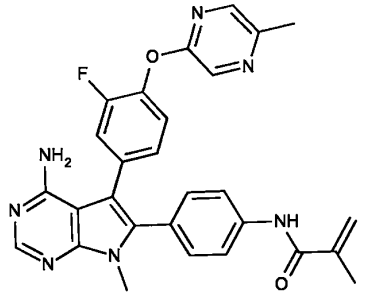
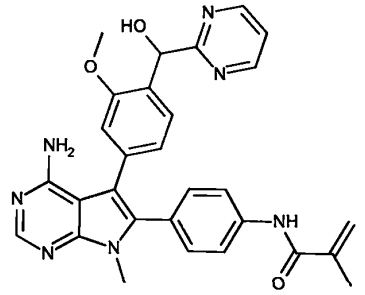
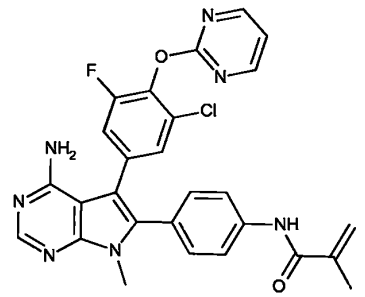
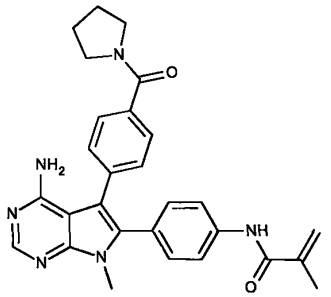
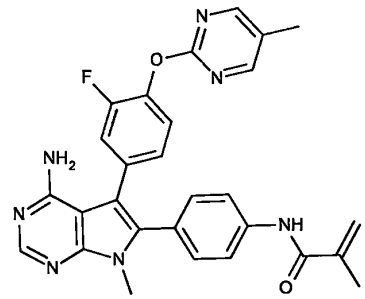
[0435]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
82		A	
83		A	A
84		A	
85		B	
86		D	C

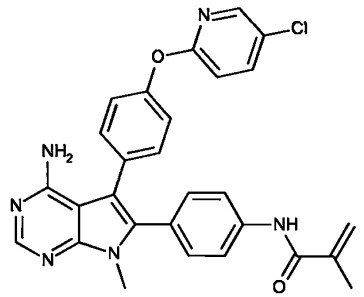
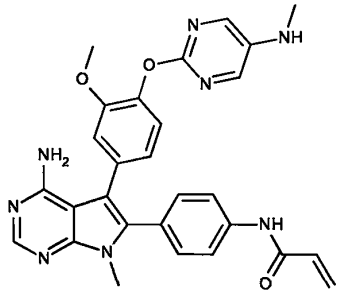
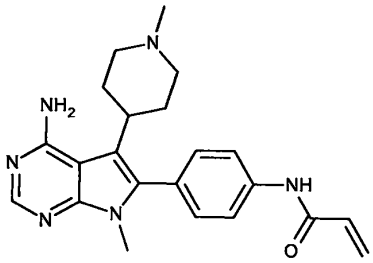
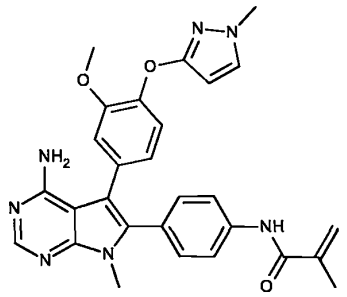
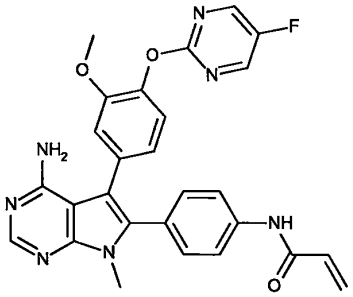
[0436]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
87		A	
88		B	
89		A	
90		A	A
91		A	A

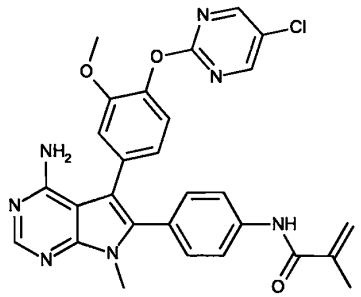
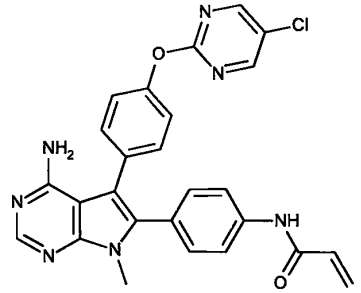
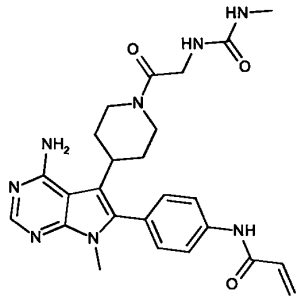
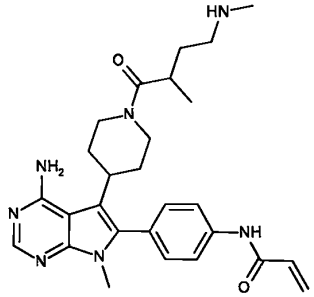
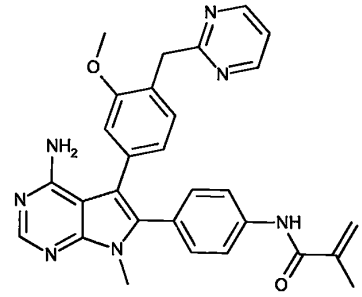
[0437]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
92		D	
93		C	
94		A	A
95		B	A
96		A	A

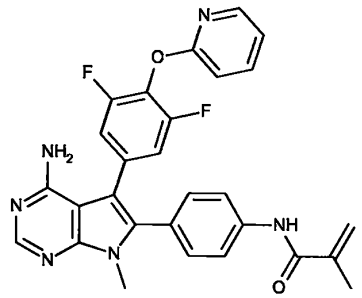
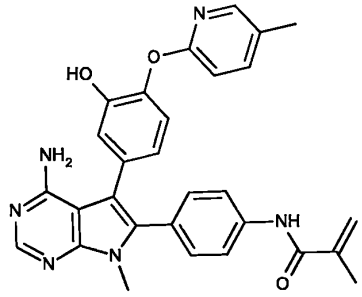
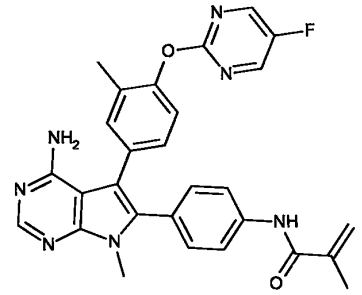
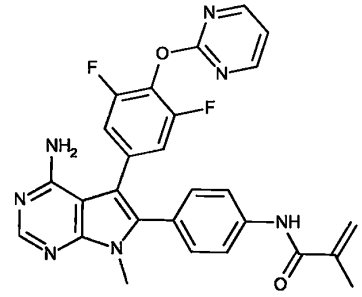
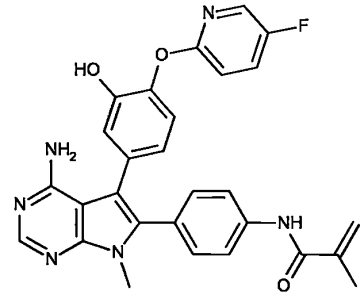
[0438]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
97		C	
98		A	A
99		D	
100		C	B
101		A	A

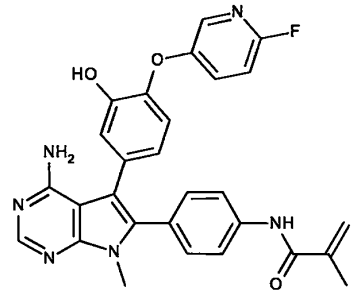
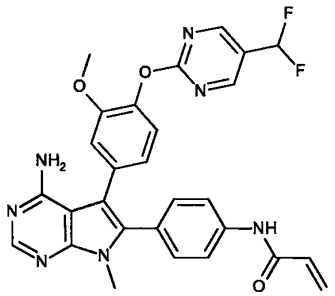
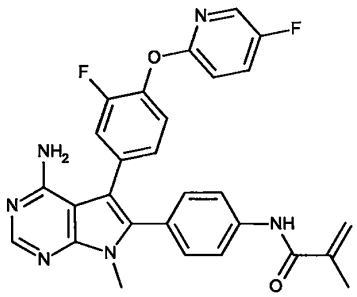
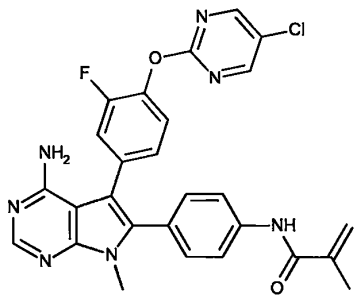
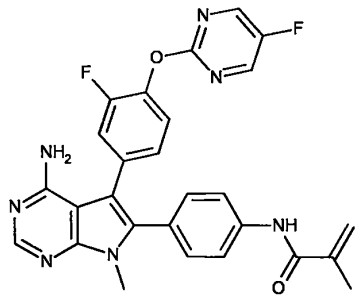
[0439]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
102		B	
103		A	A
104		D	
105		C	
106		D	

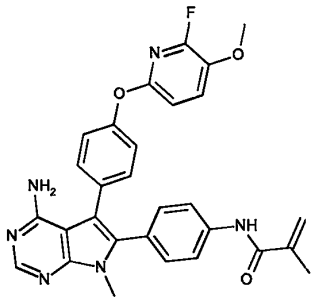
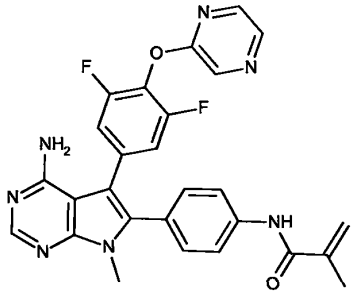
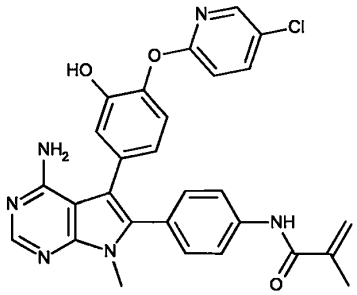
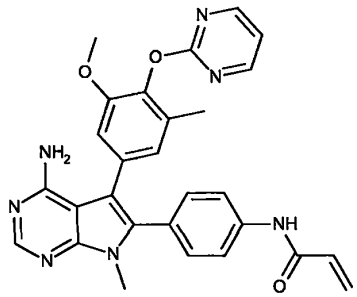
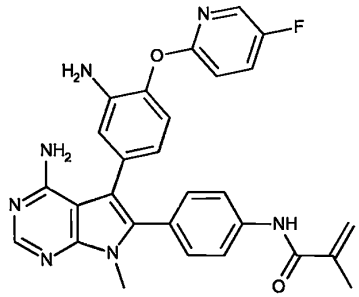
[0440]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
107		C	
108		D	
109		B	
110		A	A
111		D	

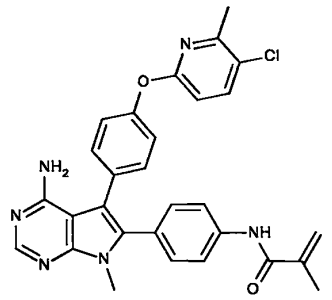
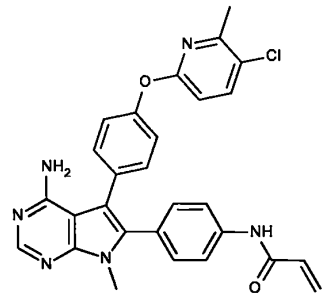
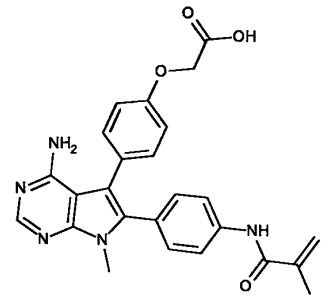
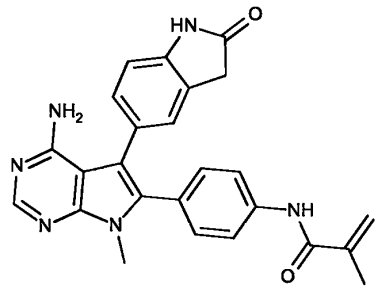
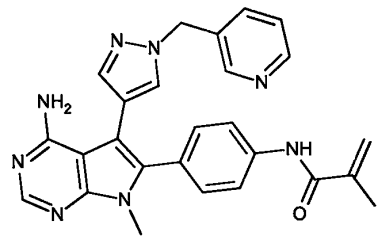
[0441]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
112		D	
113		A	A
114		C	B
115		C	
116		A	A

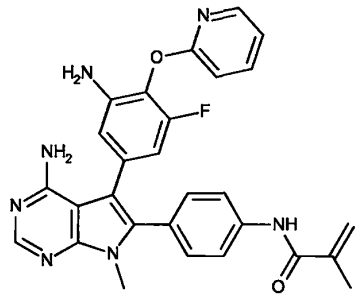
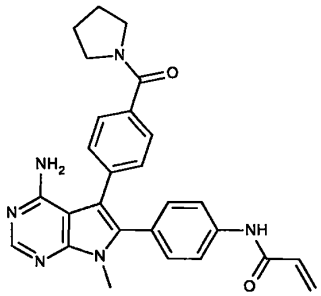
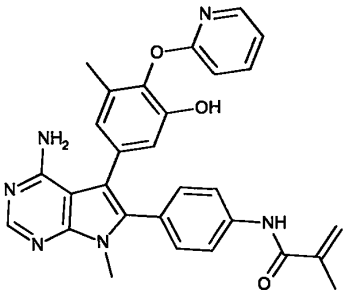
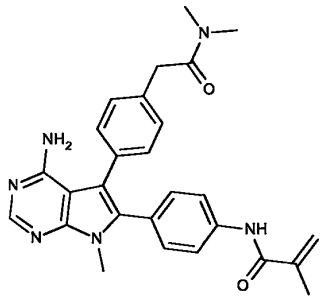
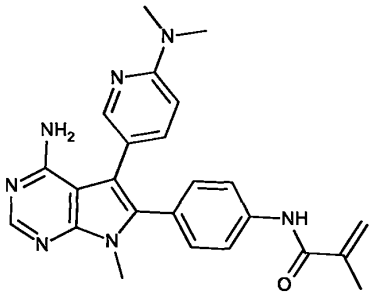
[0442]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
117		C	B
118		D	
119		D	
120		A	A
121			

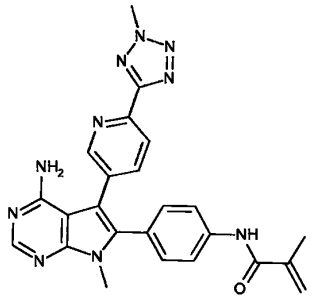
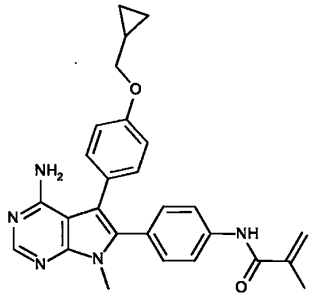
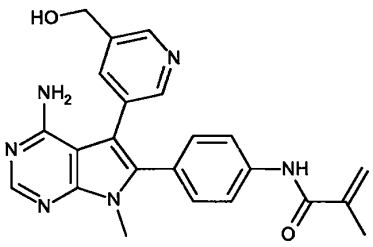
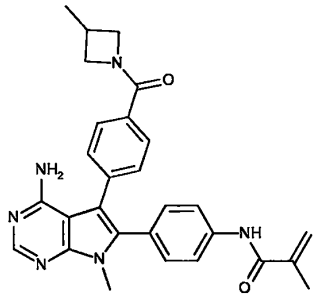
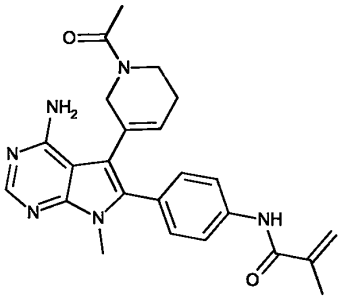
[0443]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
122		C	
123		A	A
124		D	
125		D	
126		D	

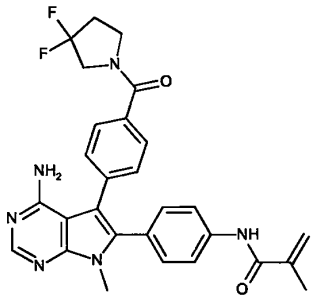
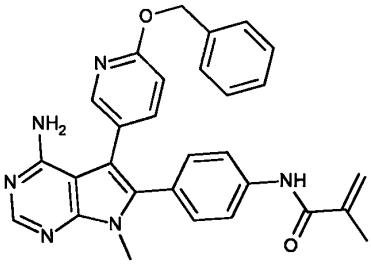
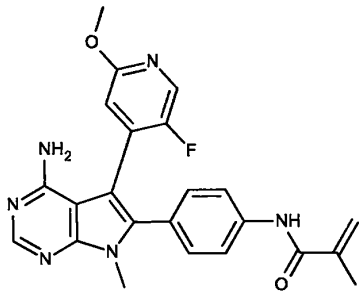
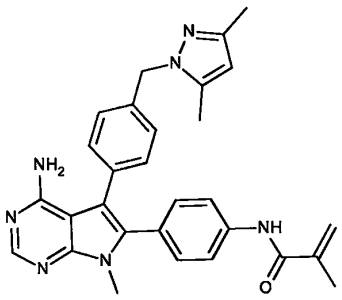
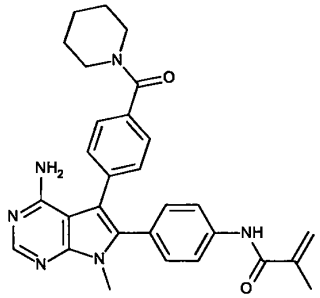
[0444]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
127		B	
128		A	A
129		C	
130		D	
131		D	

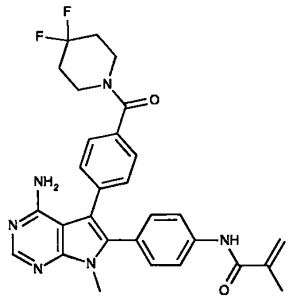
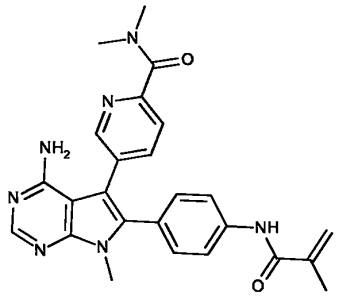
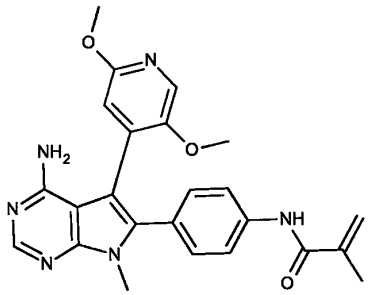
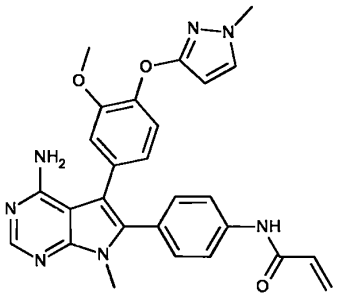
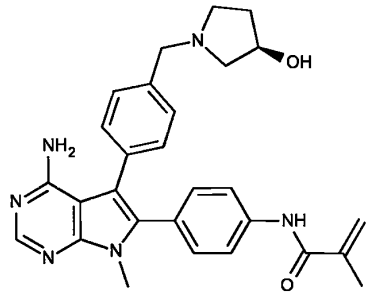
[0445]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
132		D	
133		B	
134		D	
135		C	B
136		D	

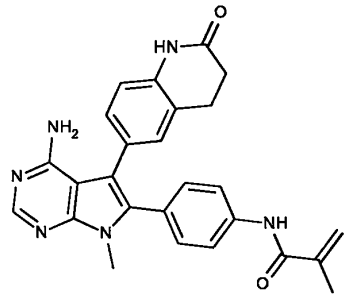
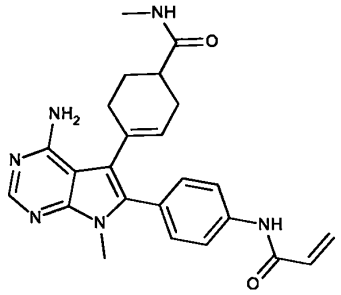
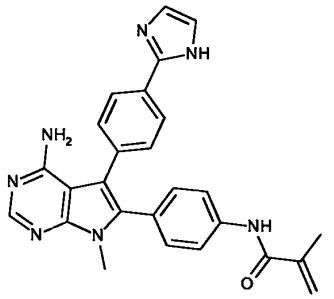
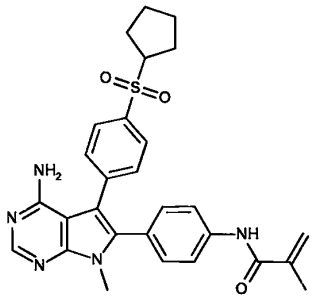
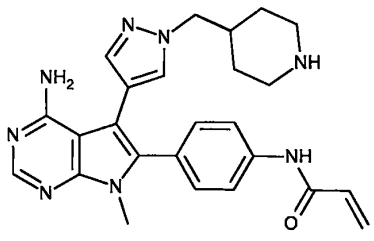
[0446]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
137		C	A
138		D	
139		D	
140		C	B
141		A	A

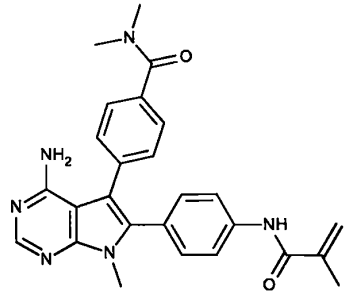
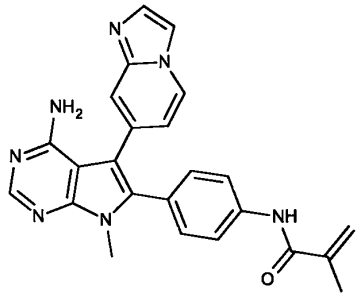
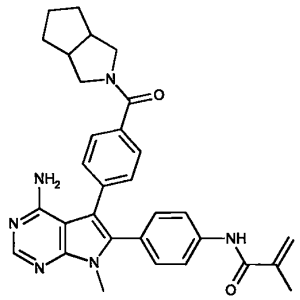
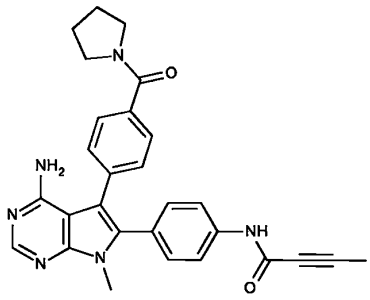
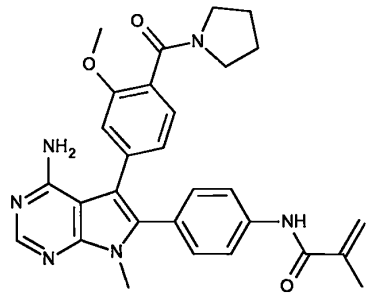
[0447]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
142		D	
143		D	C
144		D	
145		A	A
146		D	

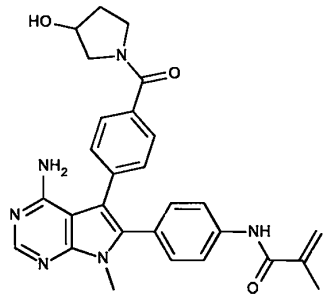
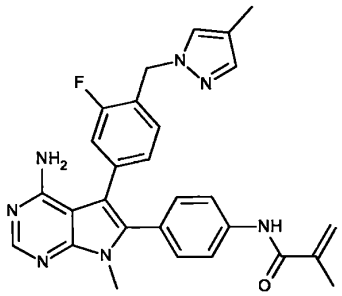
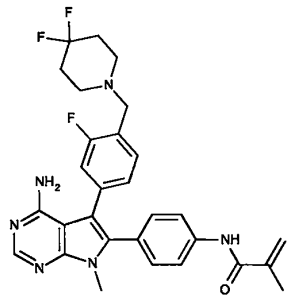
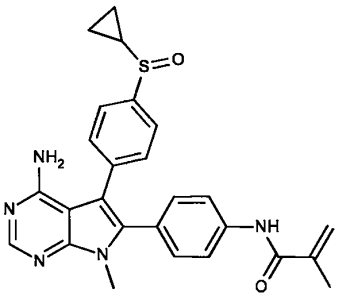
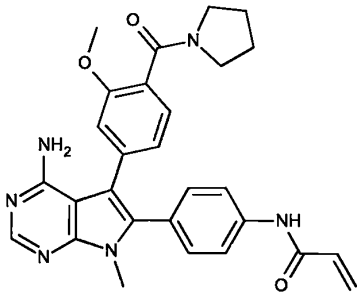
[0448]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
147		D	
148		A	A
149		C	
150		A	A
151		C	

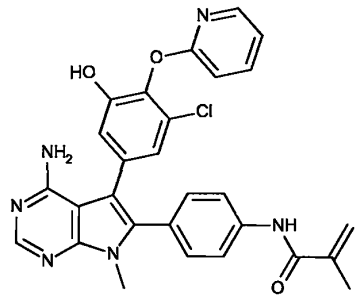
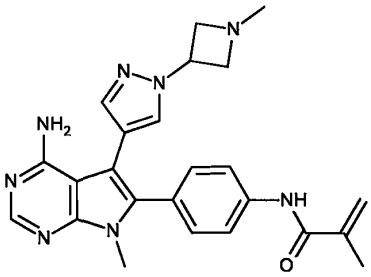
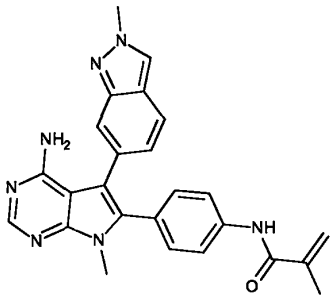
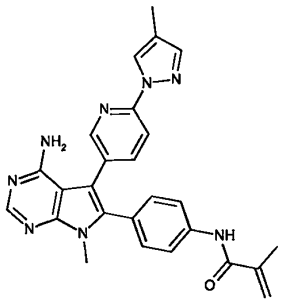
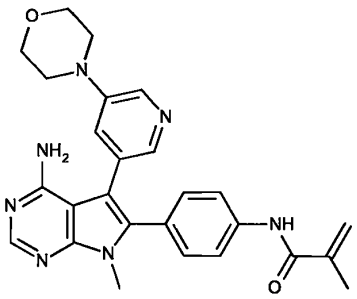
[0449]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
152		C	C
153		D	
154		B	A
155		A	A
156		C	B

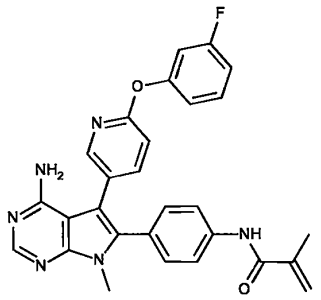
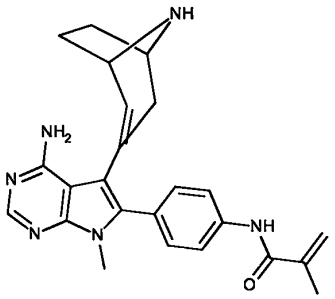
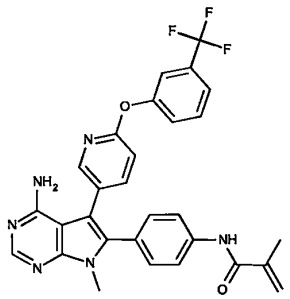
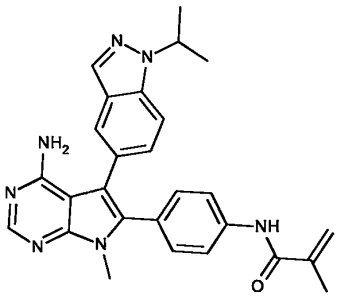
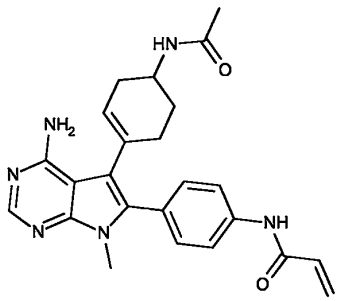
[0450]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
157		C	C
158		D	
159		D	
160		C	C
161		A	A

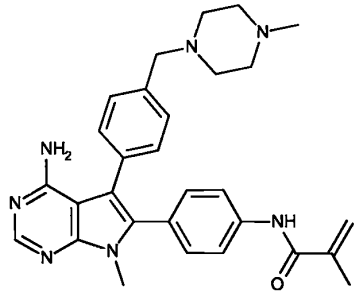
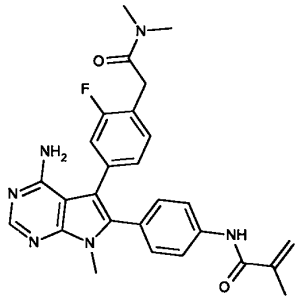
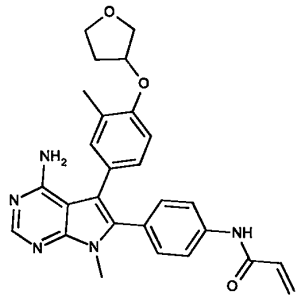
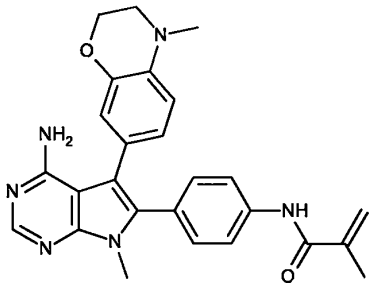
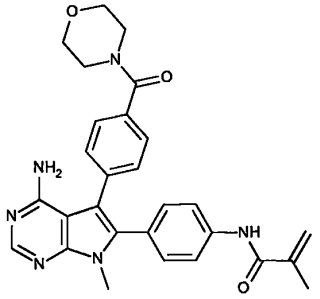
[0451]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
162		C	
163		D	
164		B	
165		C	
166		D	C

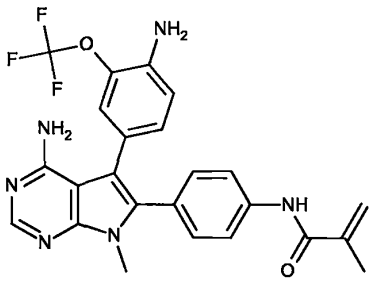
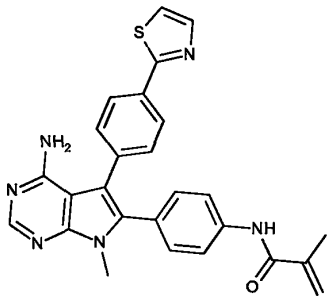
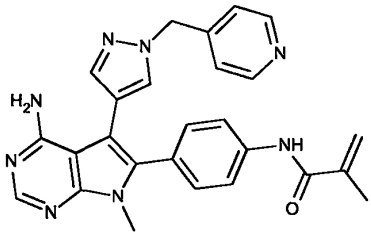
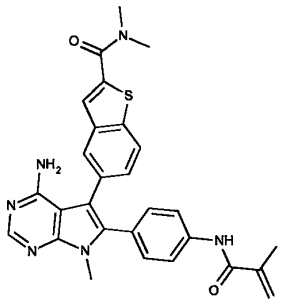
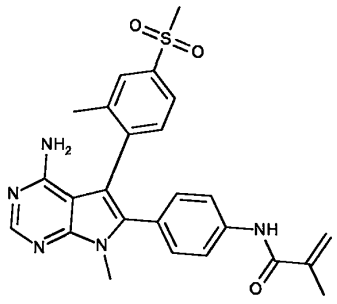
[0452]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
167		D	B
168		B	
169		D	C
170		C	
171		B	C

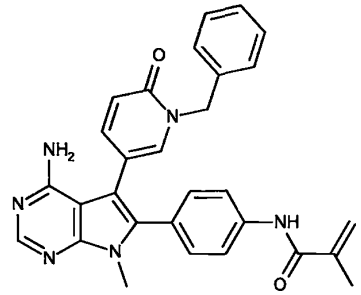
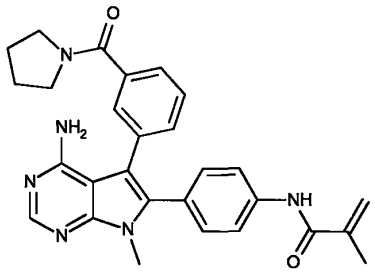
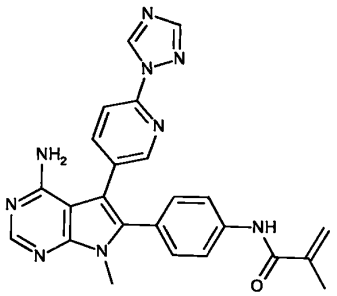
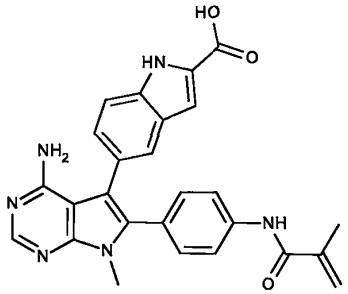
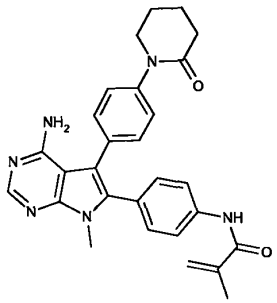
[0453]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
172		D	
173		D	
174		A	A
175		A	
176		D	C

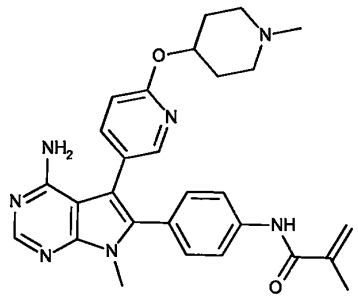
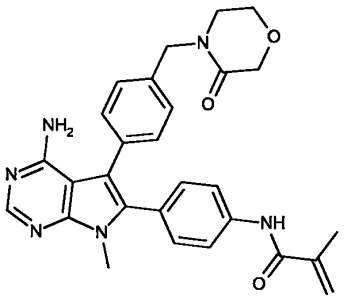
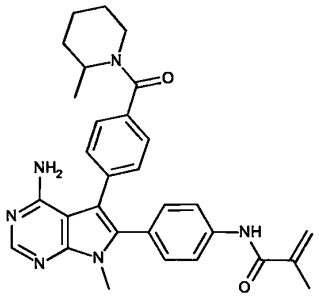
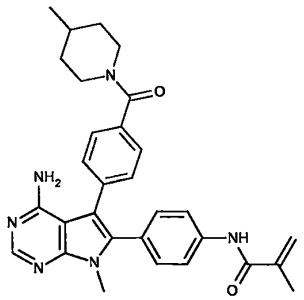
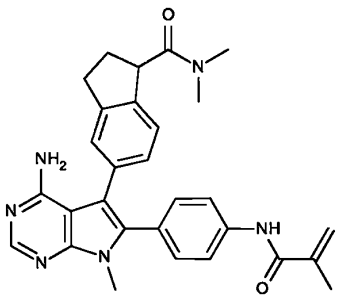
[0454]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
177		D	
178		C	
179		D	
180		C	B
181		D	

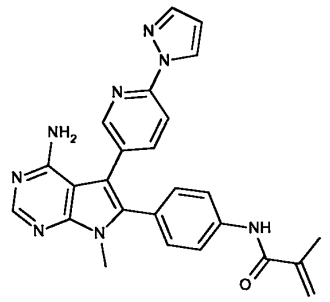
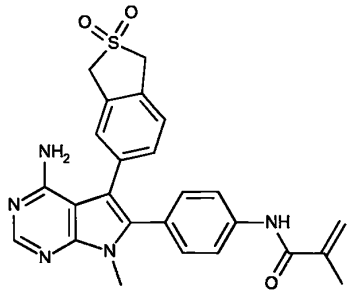
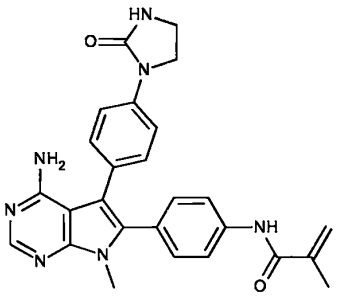
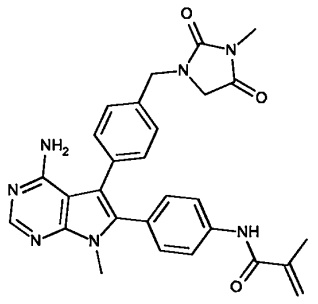
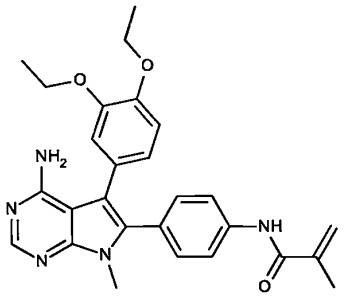
[0455]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
182		D	
183		D	
184		D	
185		D	
186		D	C

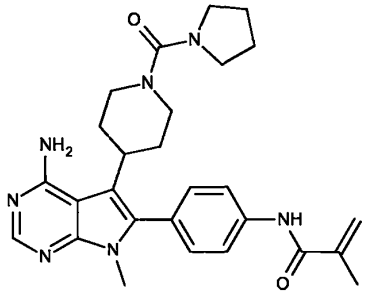
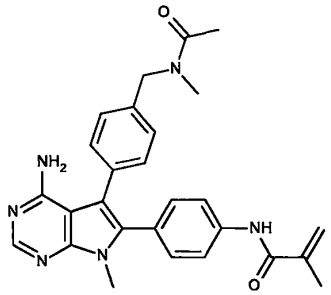
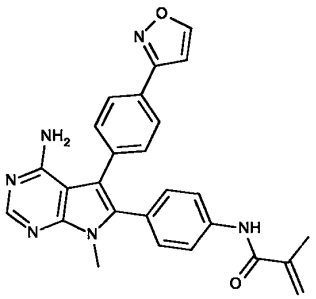
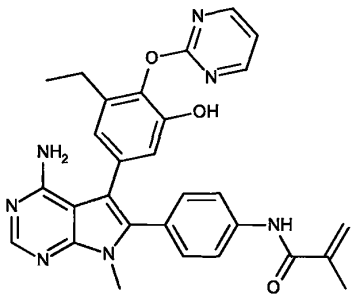
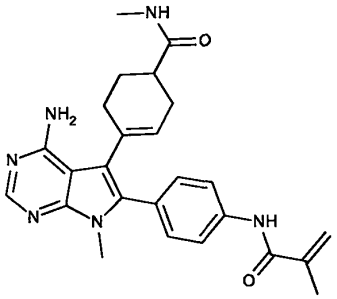
[0456]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
187		D	
188		D	C
189		A	A
190		D	C
191		D	

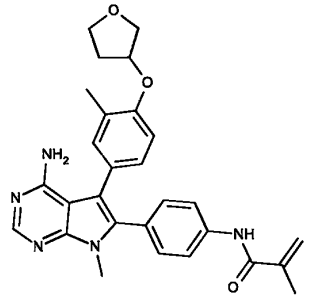
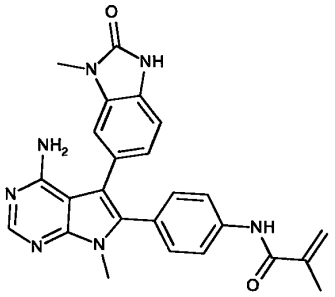
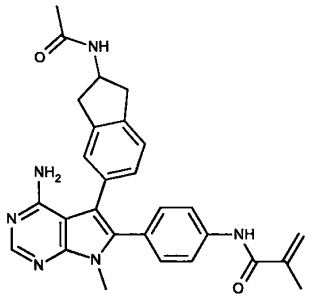
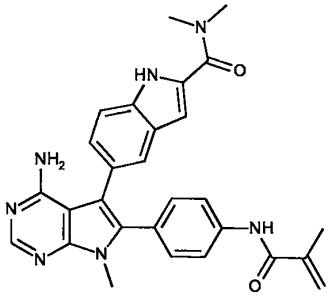
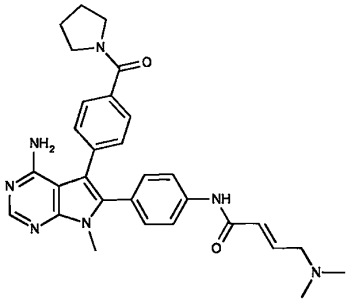
[0457]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
192		D	
193		D	
194		C	C
195			
196		D	

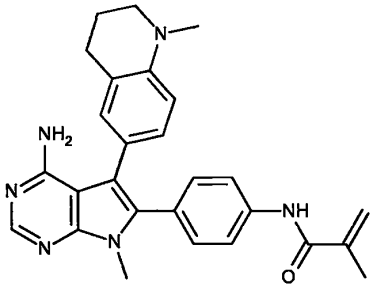
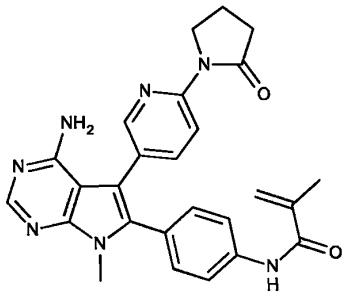
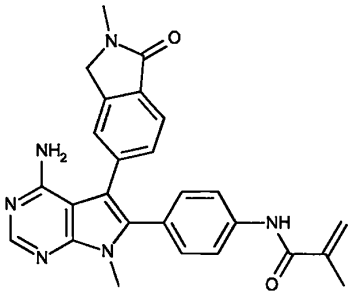
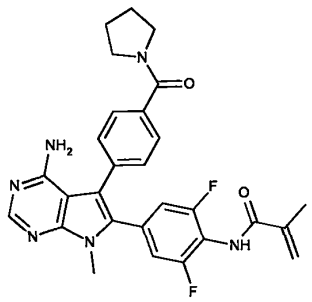
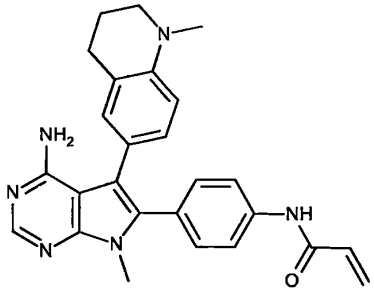
[0458]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
197		D	C
198		D	
199		C	C
200		D	
201		D	C

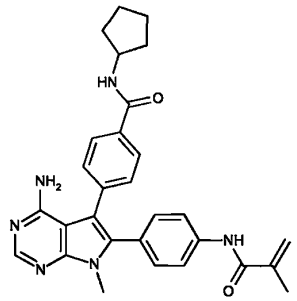
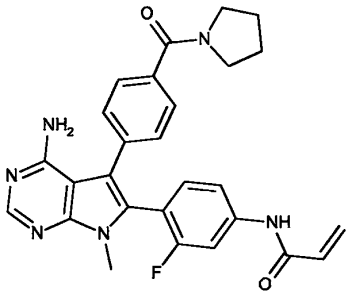
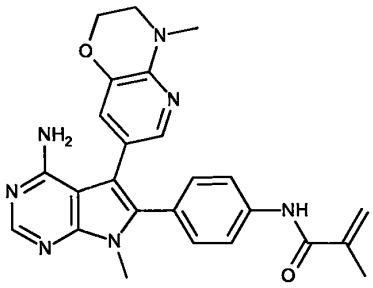
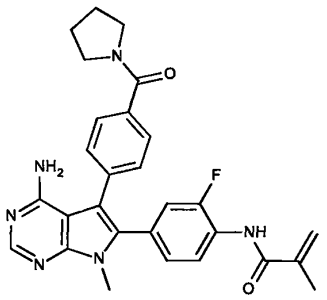
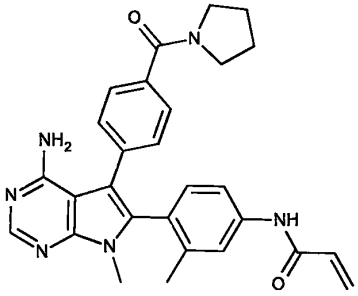
[0459]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
202		C	B
203		D	
204		D	
205		D	
206		A	B

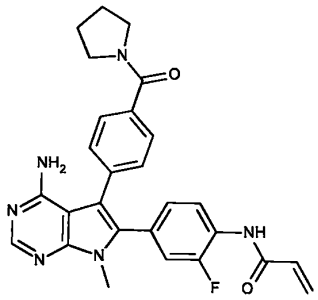
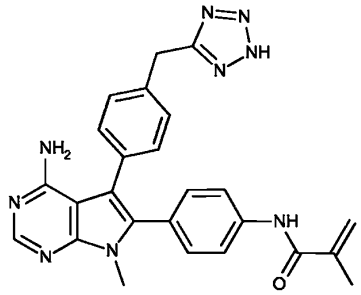
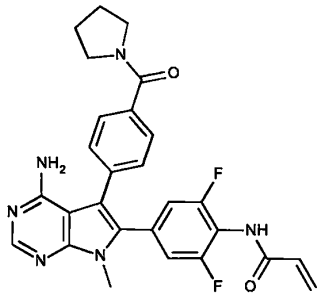
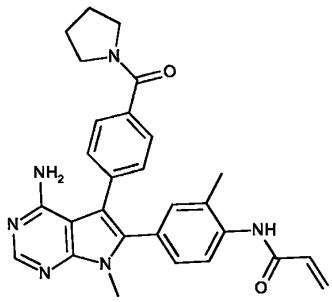
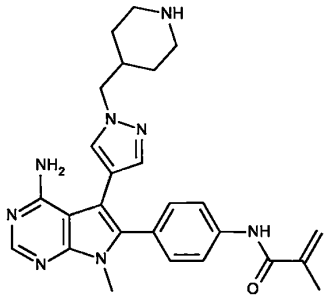
[0460]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
207		C	C
208		D	
209		D	
210		D	C
211		A	A

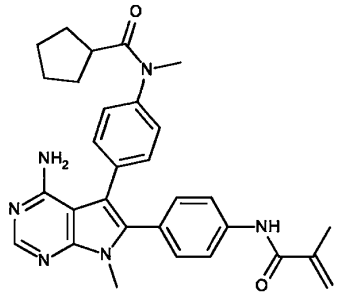
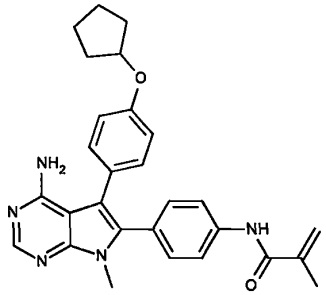
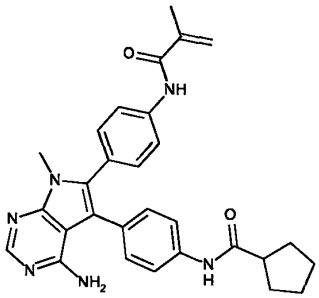
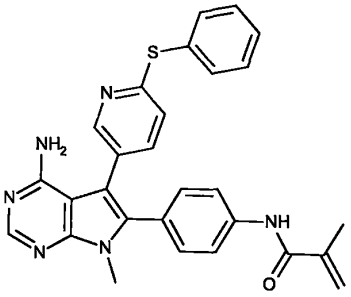
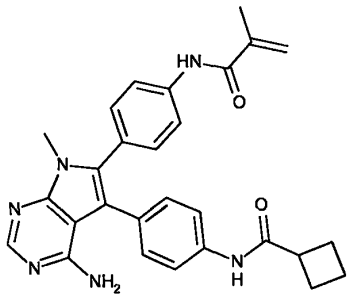
[0461]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
212		A	A
213		A	A
214		B	
215		C	C
216		A	A

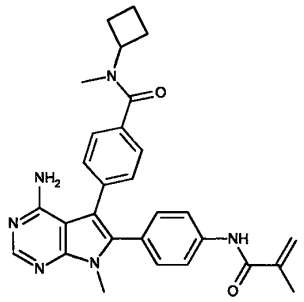
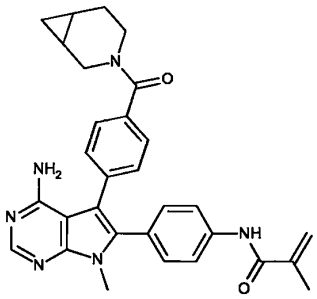
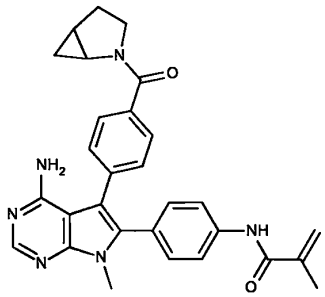
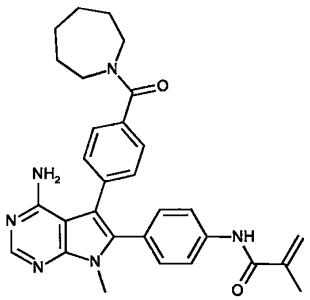
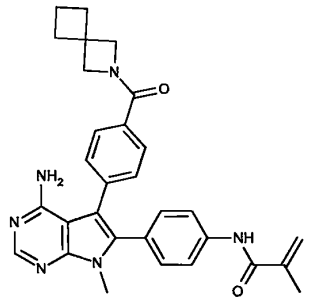
[0462]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
217		A	A
218		D	
219		A	A
220		A	A
221		D	

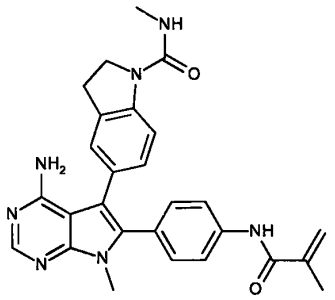
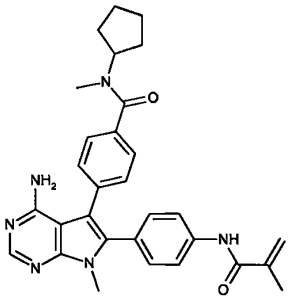
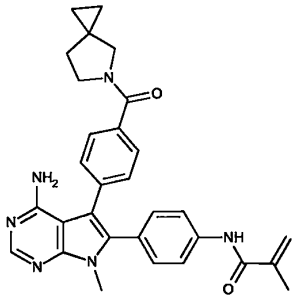
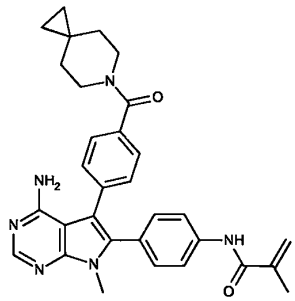
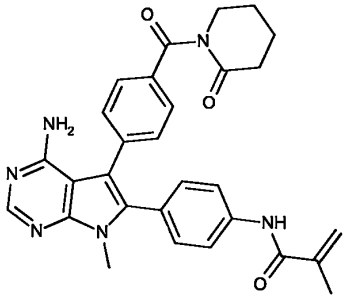
[0463]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
222		D	
223		A	A
224		A	A
225		C	
226		A	

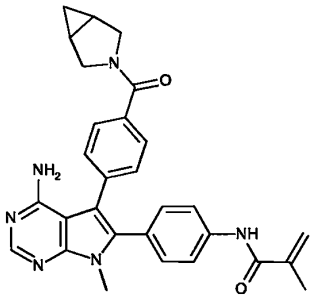
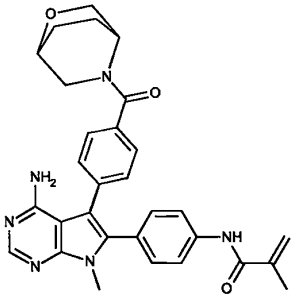
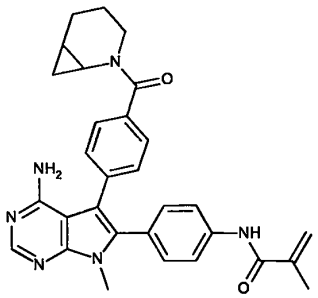
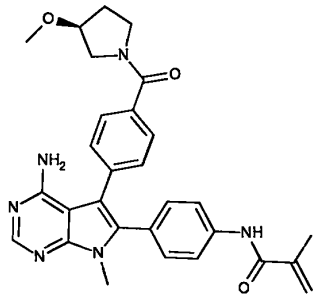
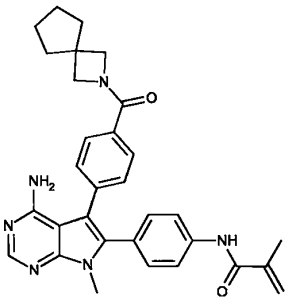
[0464]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
227		B	B
228		A	A
229		A	A
230		A	A
231		D	

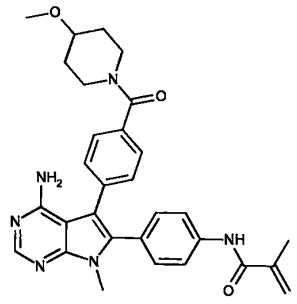
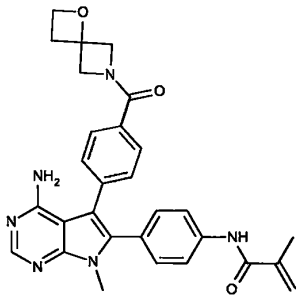
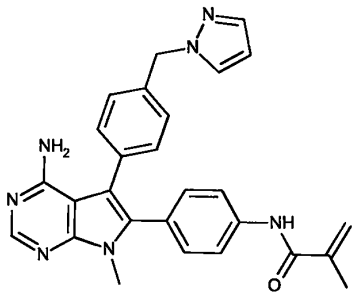
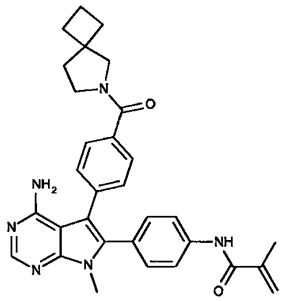
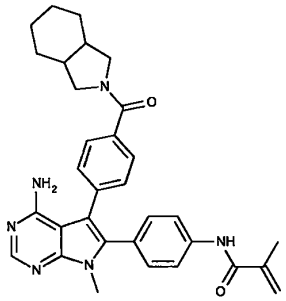
[0465]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
232		C	
233		B	B
234		A	A
235			
236		B	B

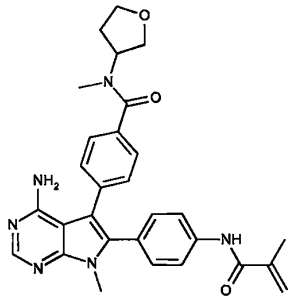
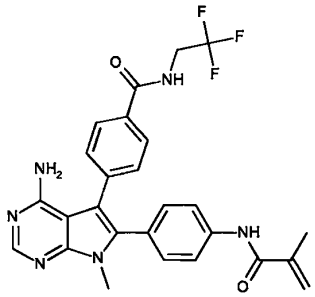
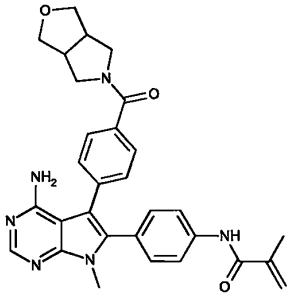
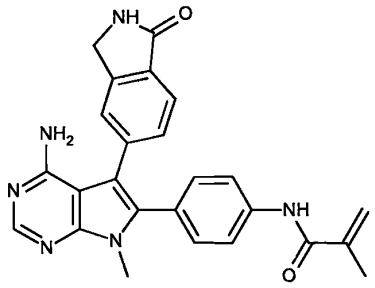
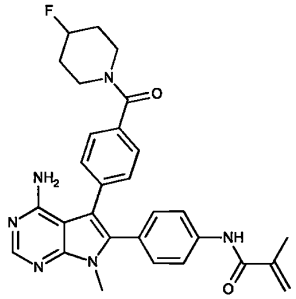
[0466]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
237		B	B
238		C	C
239		A	A
240		D	
241		D	C

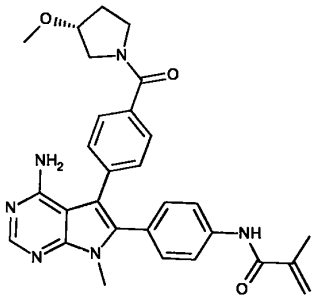
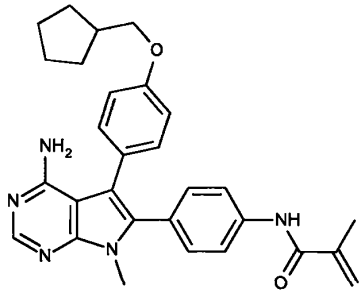
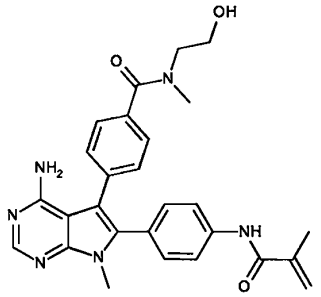
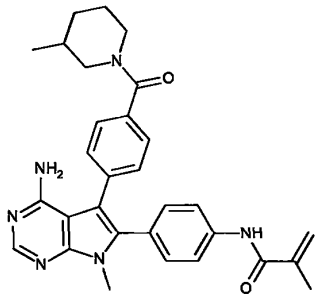
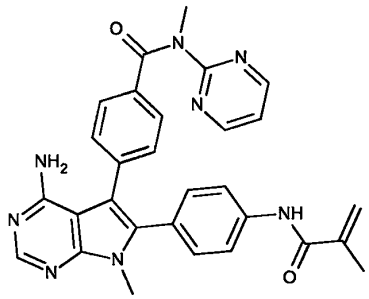
[0467]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
242		D	
243		D	
244		D	C
245		C	C
246		C	B

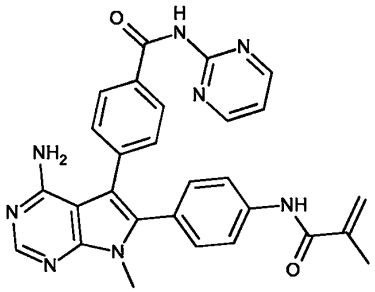
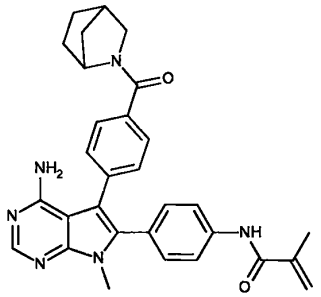
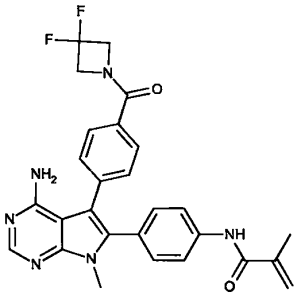
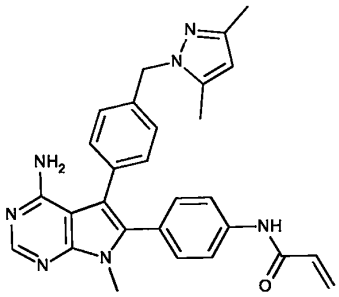
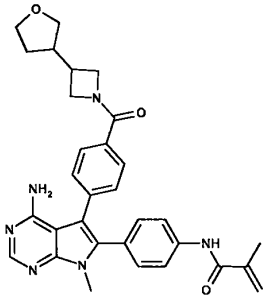
[0468]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
247		D	
248		A	A
249		C	C
250		D	
251		C	

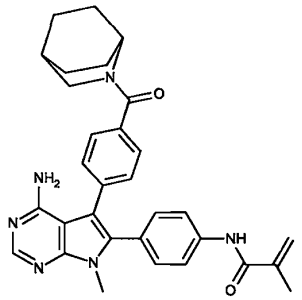
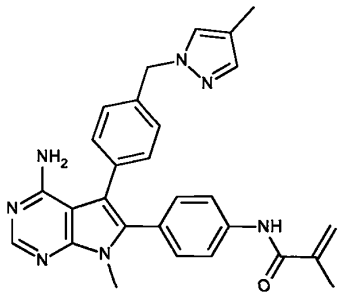
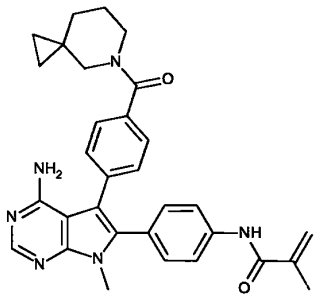
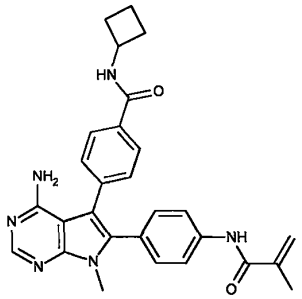
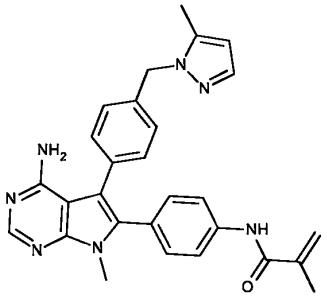
[0469]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
252		C	
253		C	
254		C	
255		A	A
256		D	

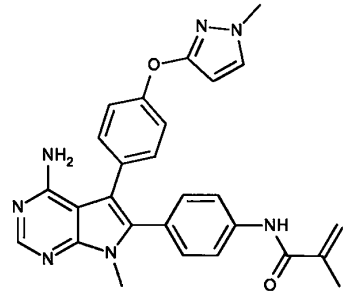
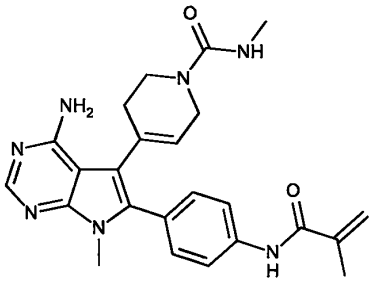
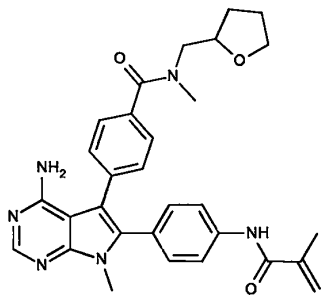
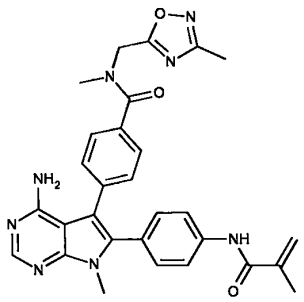
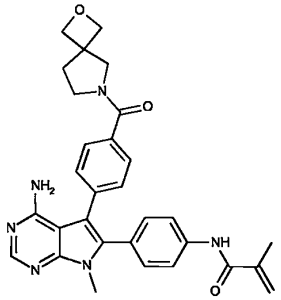
[0470]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
257		C	C
258		A	A
259		D	
260		A	A
261		D	

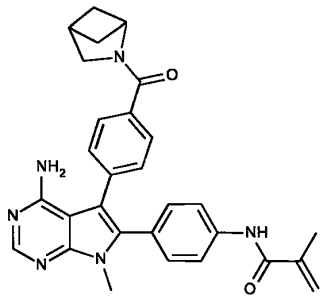
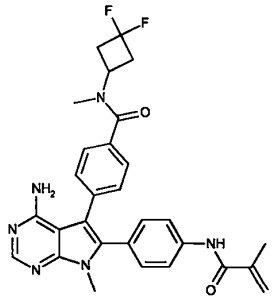
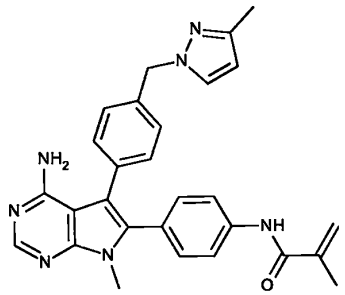
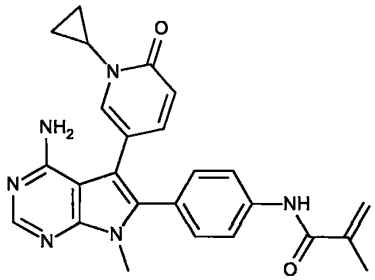
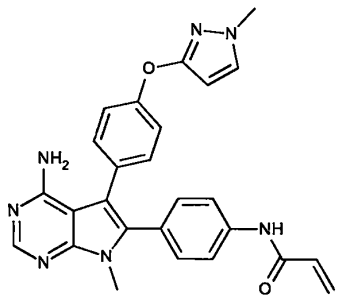
[0471]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
262		A	A
263		D	C
264		B	A
265		A	A
266		D	C

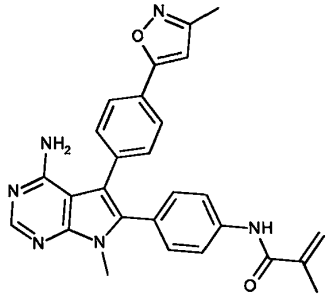
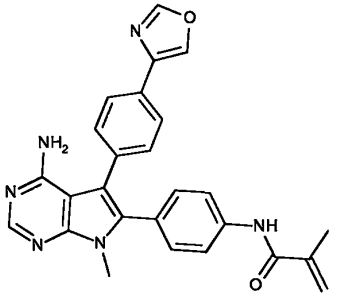
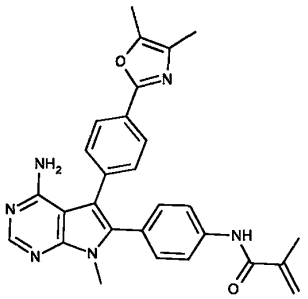
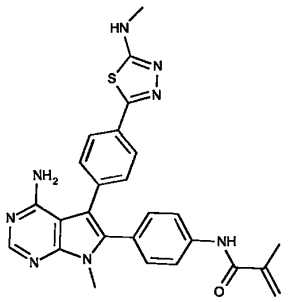
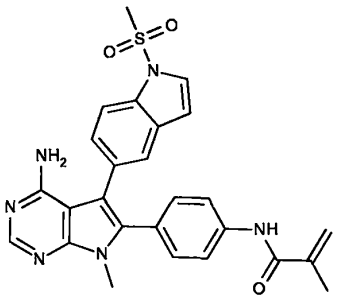
[0472]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
267		A	A
268		D	
269		D	
270		C	C
271		D	

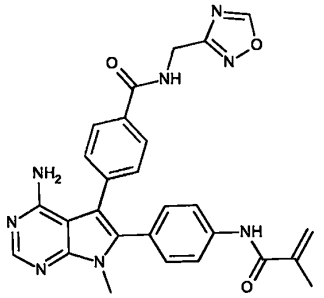
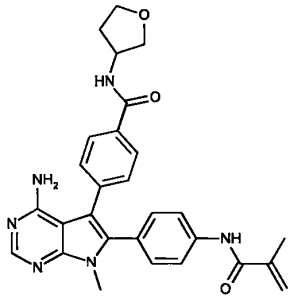
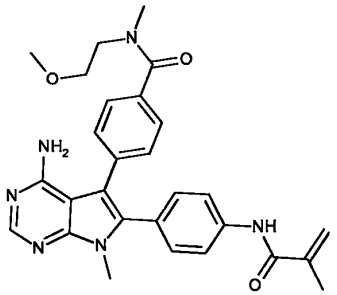
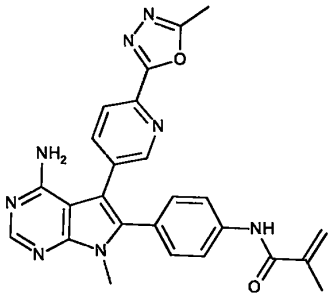
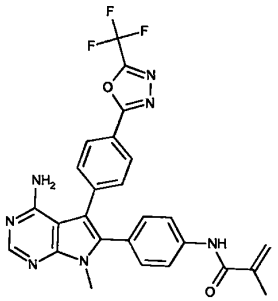
[0473]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
272		A	A
273		C	
274		B	C
275		D	
276		A	A

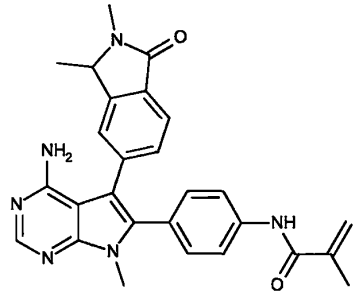
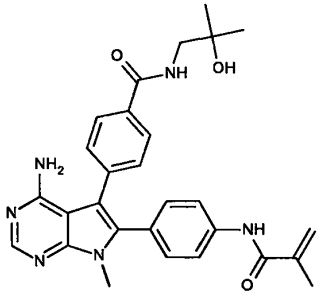
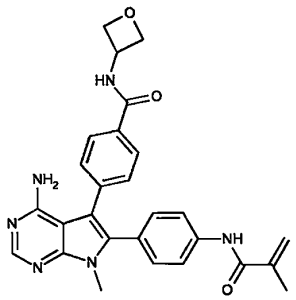
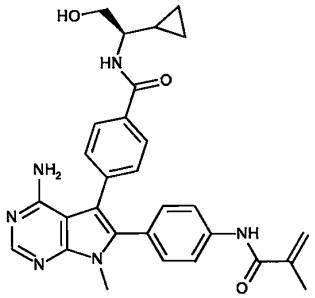
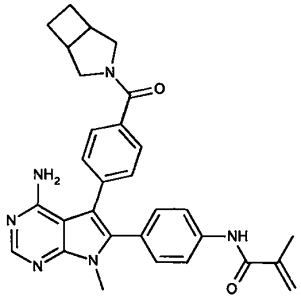
[0474]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
277		C	
278		C	
279		B	
280		B	
281		D	

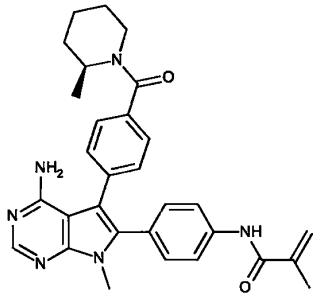
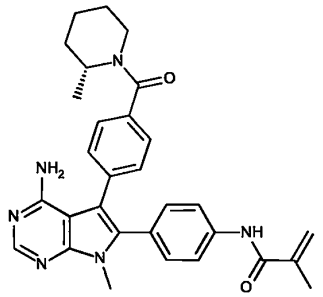
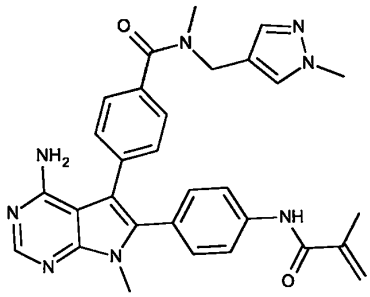
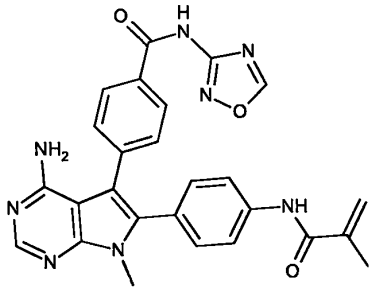
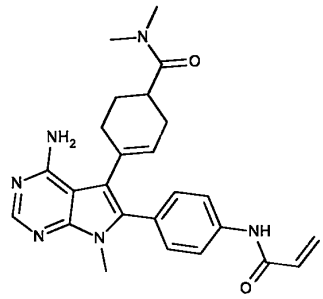
[0475]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
282		B	C
283		A	A
284		D	
285		D	
286		D	

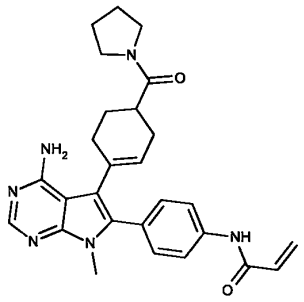
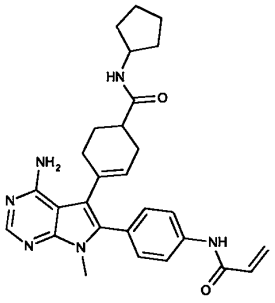
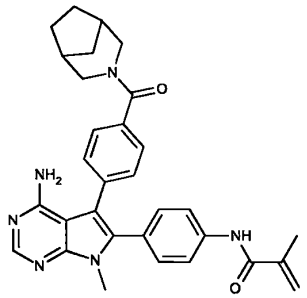
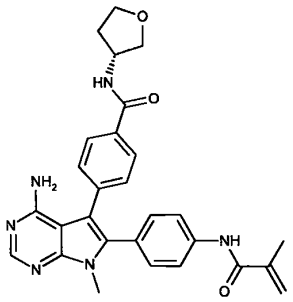
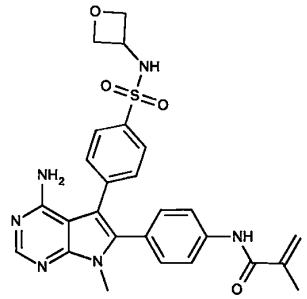
[0476]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
287		D	
288		A	C
289		C	C
290		A	B
291		A	A

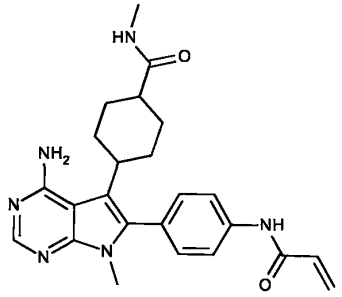
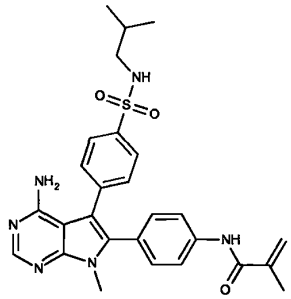
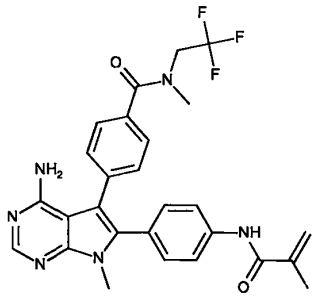
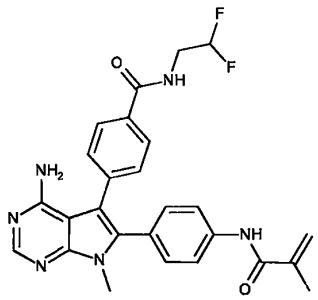
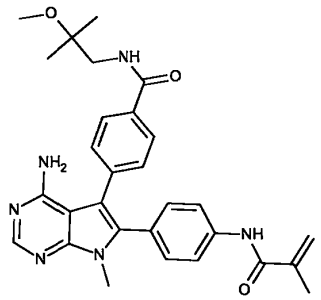
[0477]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
292		A	A
293		A	A
294		D	C
295		D	C
296		A	A

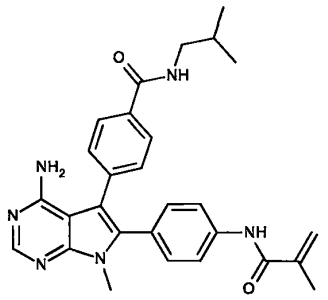
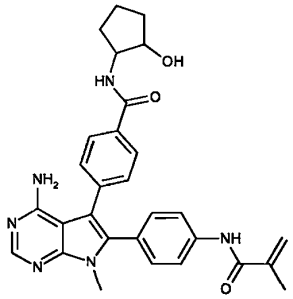
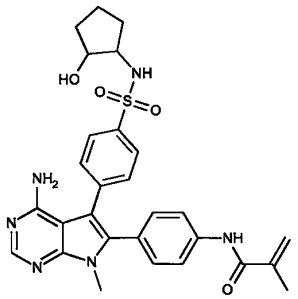
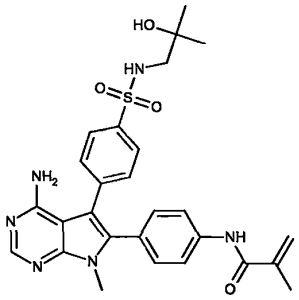
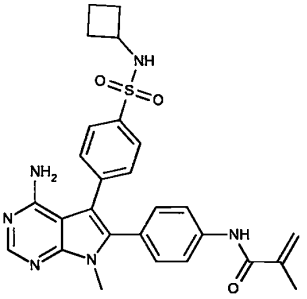
[0478]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
297		A	A
298		A	A
299		A	A
300		A	A
301		D	C

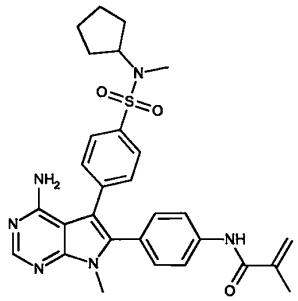
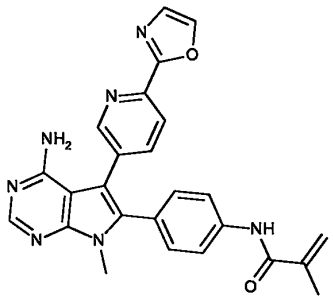
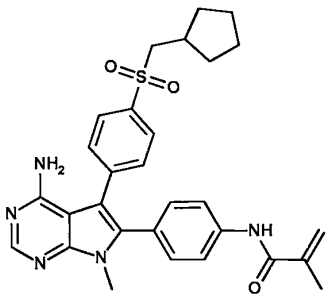
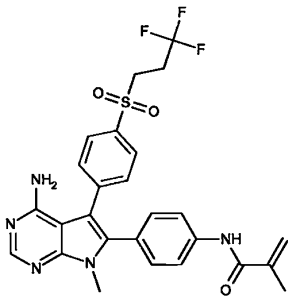
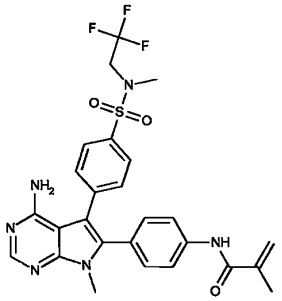
[0479]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
302		D	C
303		C	C
304		A	A
305		A	A
306		A	A

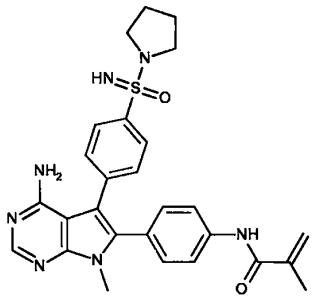
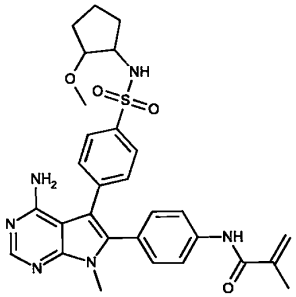
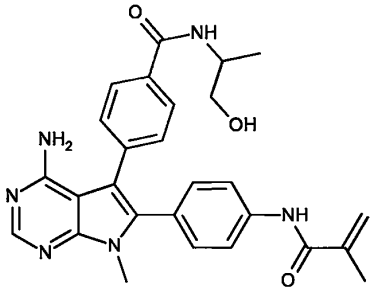
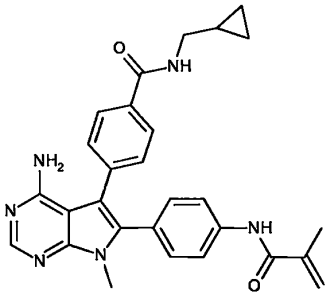
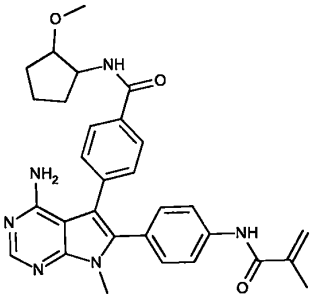
[0480]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
307		A	A
308		A	B
309		D	C
310		D	C
311		C	C

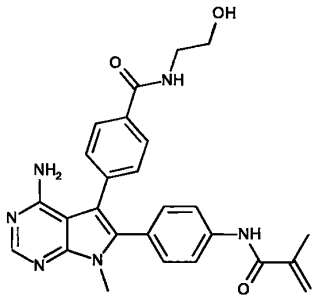
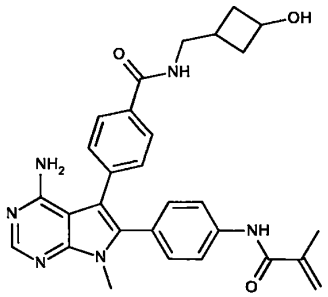
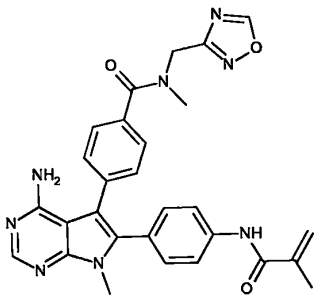
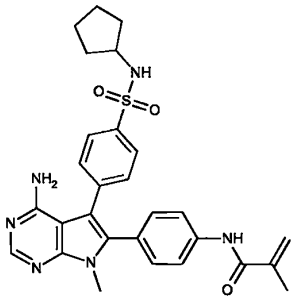
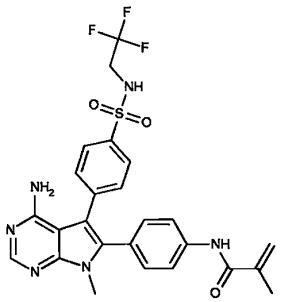
[0481]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
312		C	C
313		D	C
314		C	C
315		C	C
316		C	C

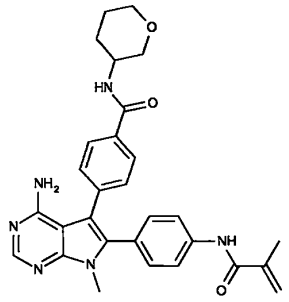
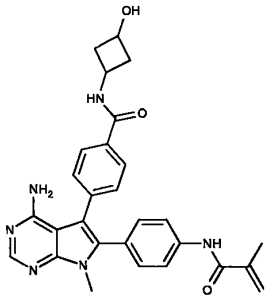
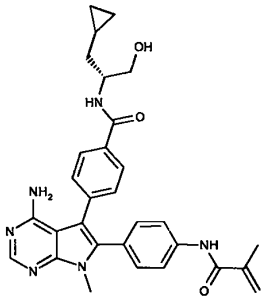
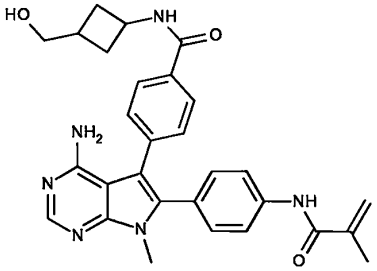
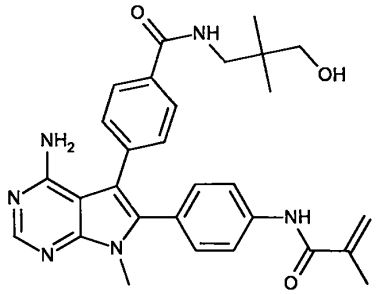
[0482]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
317		C	
318		D	C
319		A	
320		A	A
321		B	B

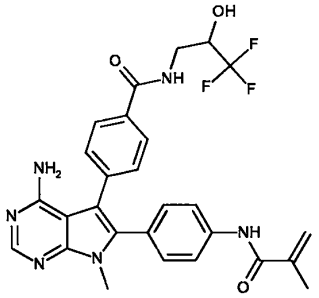
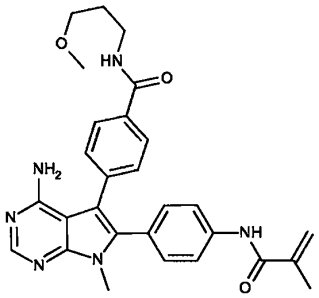
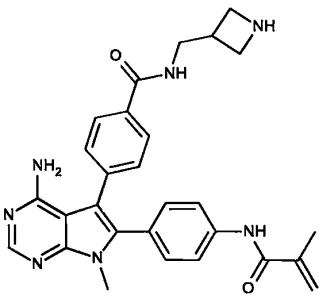
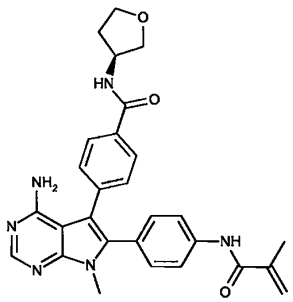
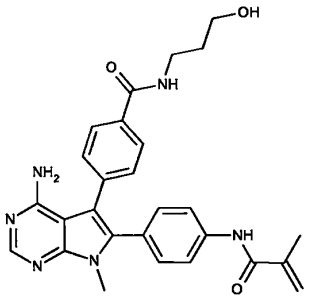
[0483]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
322		C	
323		B	
324		D	C
325		D	
326		D	

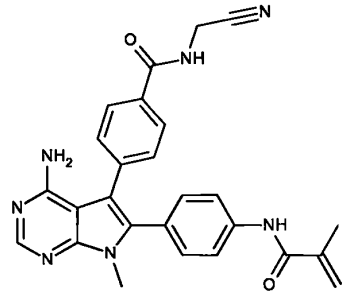
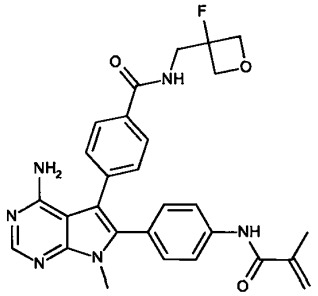
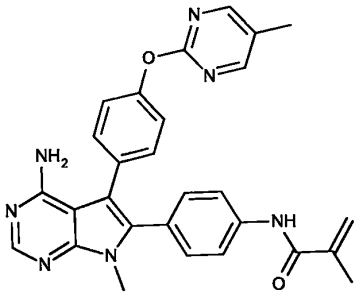
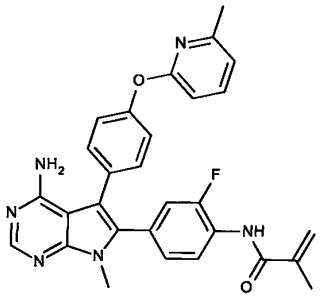
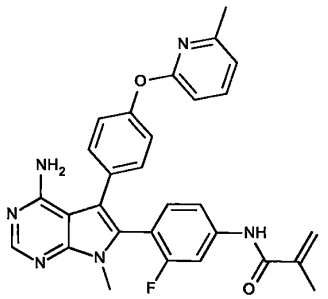
[0484]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
327		A	B
328		C	
329		A	C
330		B	
331		A	A

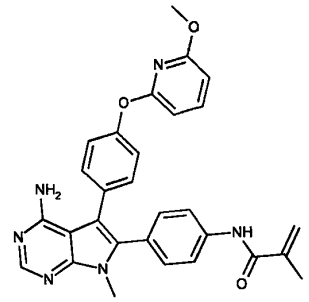
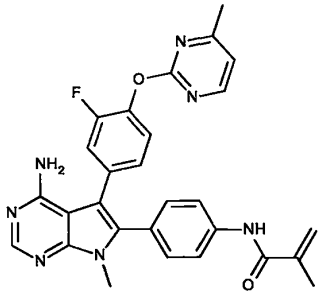
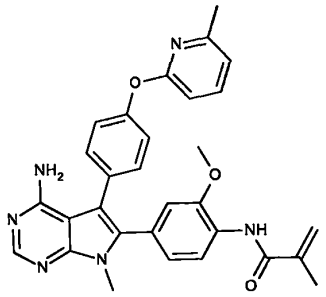
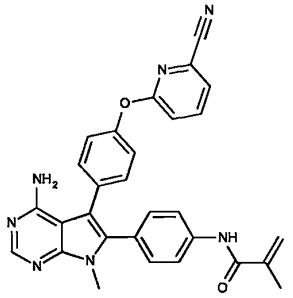
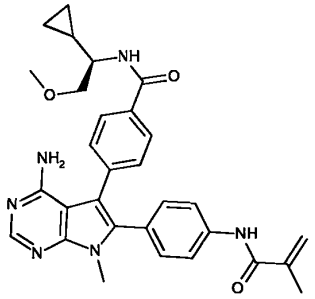
[0485]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
332		A	C
333		B	
334		C	
335		C	C
336		B	

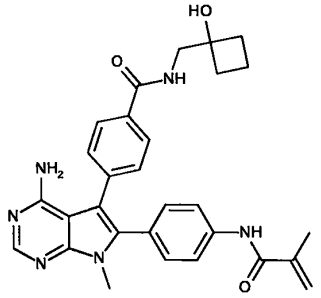
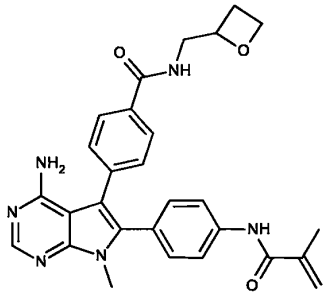
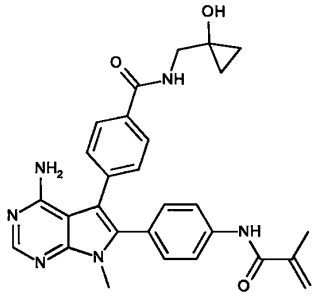
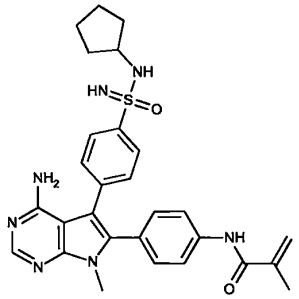
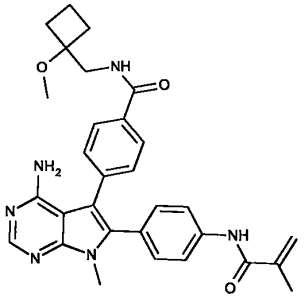
[0486]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
337		C	C
338		A	A
339		B	A
340		A	A
341		A	A

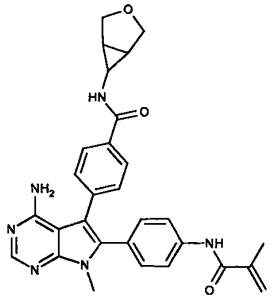
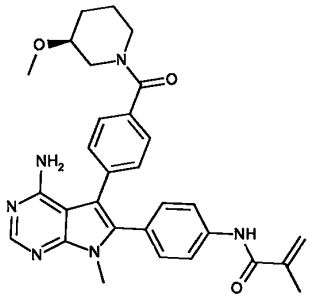
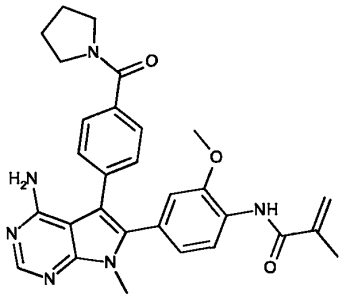
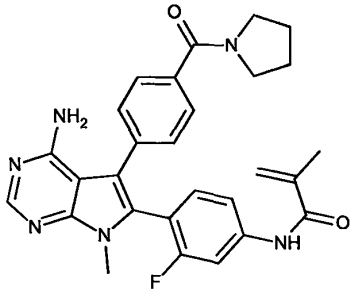
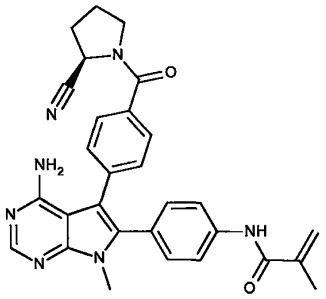
[0487]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
342		A	A
343		A	A
344		B	A
345		A	
346		A	A

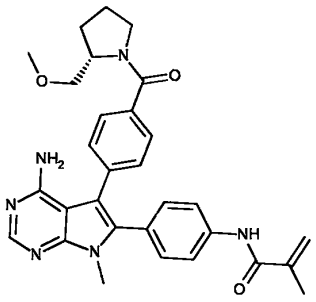
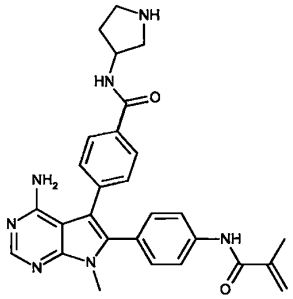
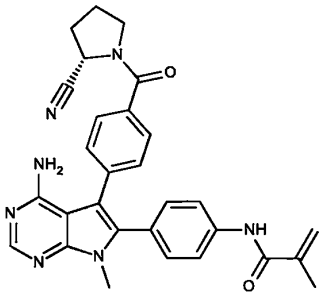
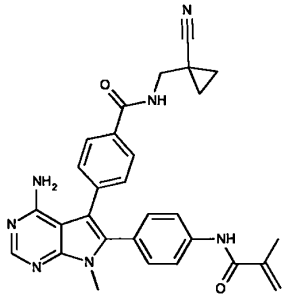
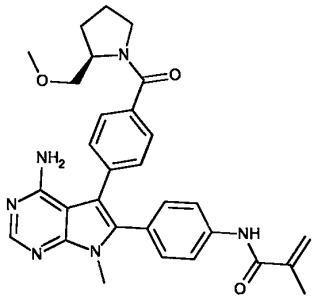
[0488]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
347		A	
348		A	C
349		A	
350		D	
351		A	A

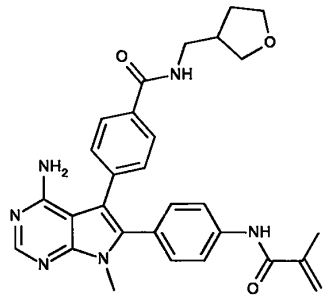
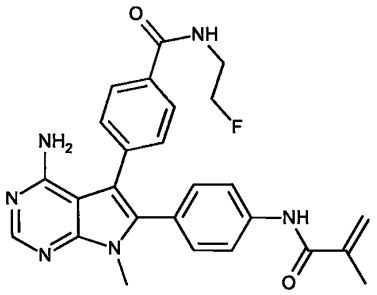
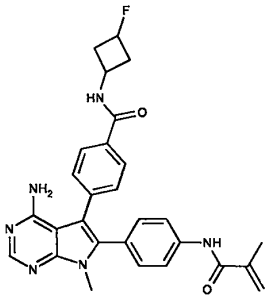
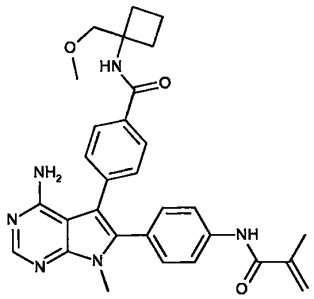
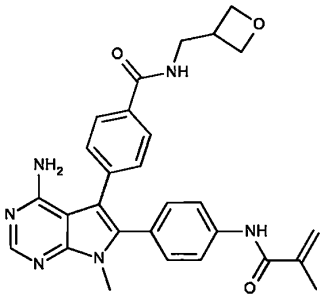
[0489]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
352		C	C
353		D	C
354		D	C
355		A	A
356		B	

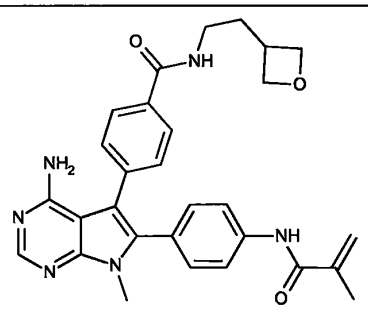
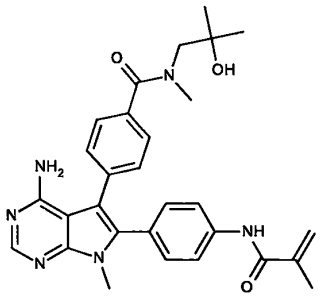
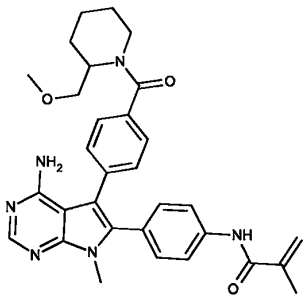
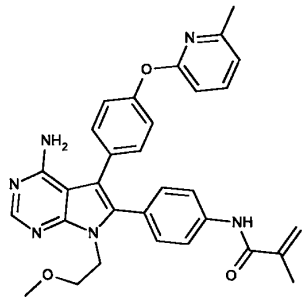
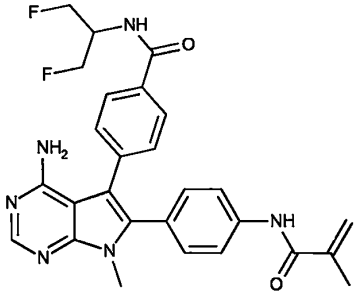
[0490]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
357		A	A
358		A	
359		A	
360		A	
361		C	C

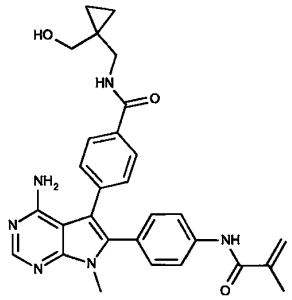
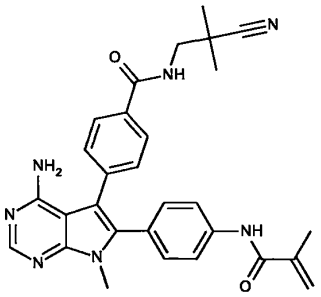
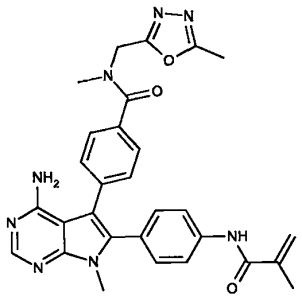
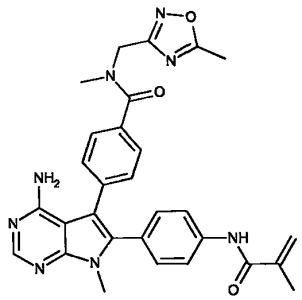
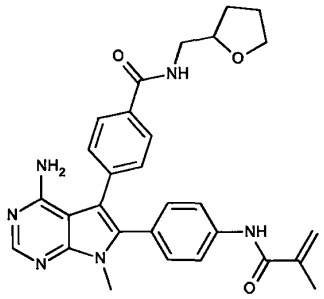
[0491]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
362		A	C
363		A	
364		A	
365		A	A
366		B	

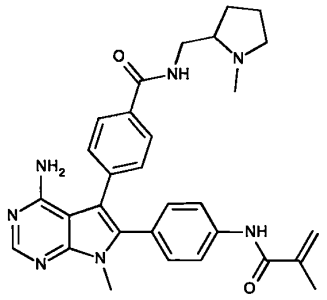
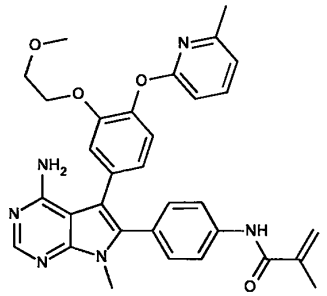
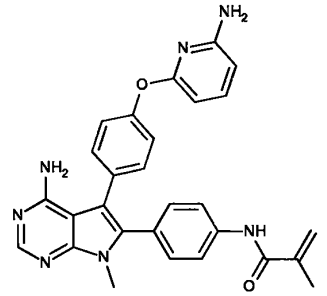
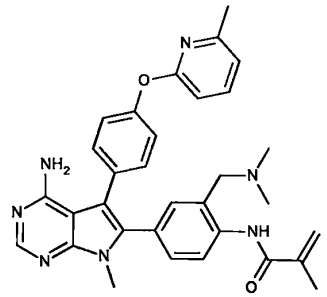
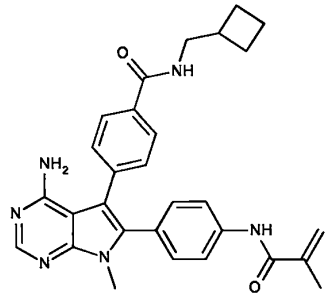
[0492]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
367		C	
368		C	C
369		A	A
370		A	A
371		A	A

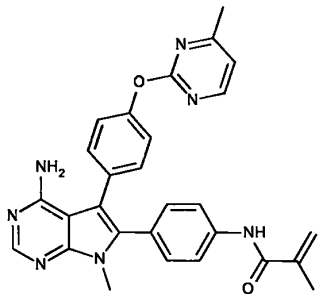
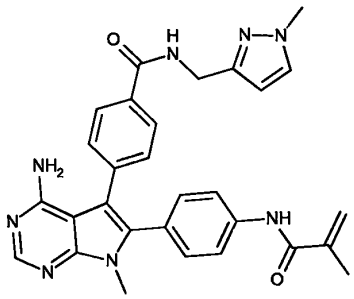
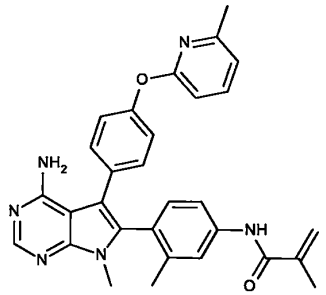
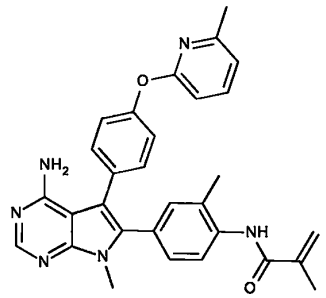
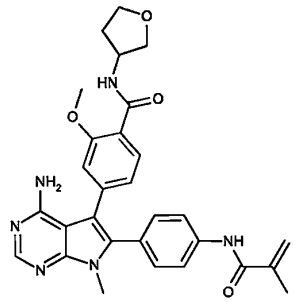
[0493]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
372		A	C
373		A	A
374		D	C
375		C	C
376		A	A

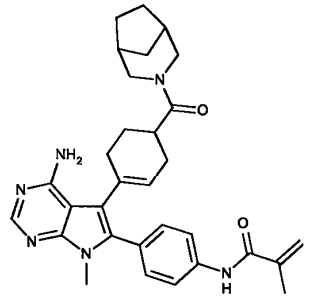
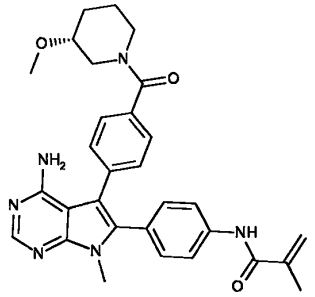
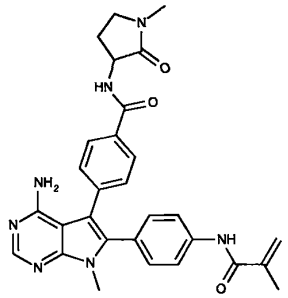
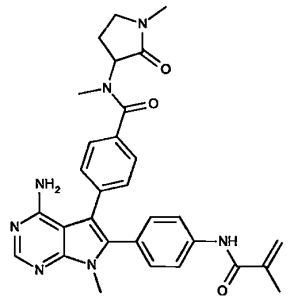
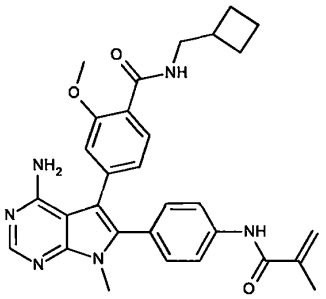
[0494]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
377		C	C
378		D	C
379		A	A
380		B	C
381		A	A

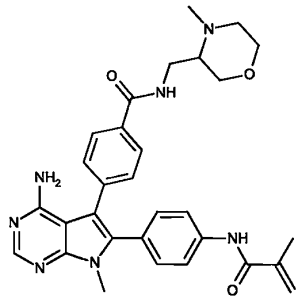
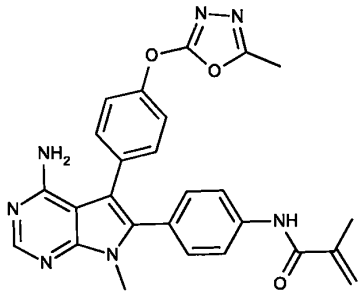
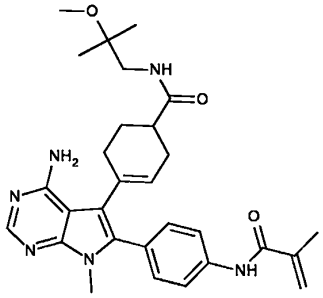
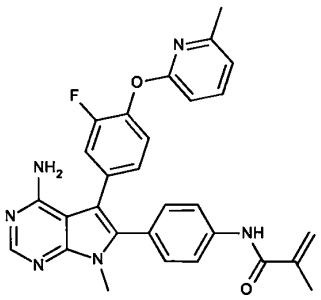
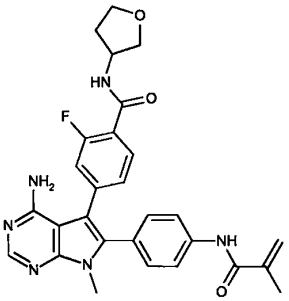
[0495]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
382		A	A
383		D	C
384		A	A
385		B	A
386		A	B

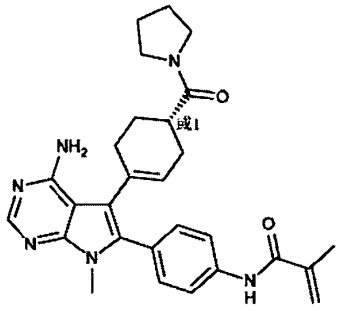
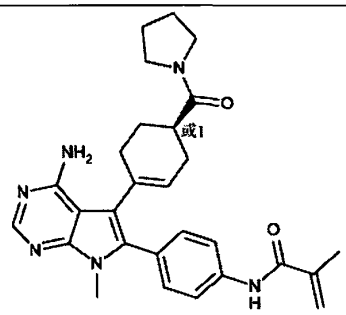
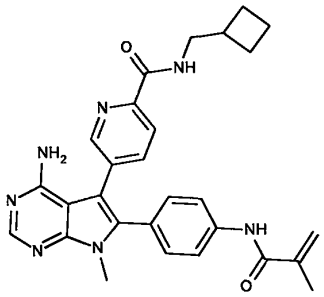
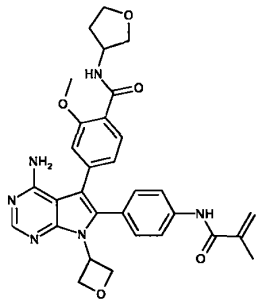
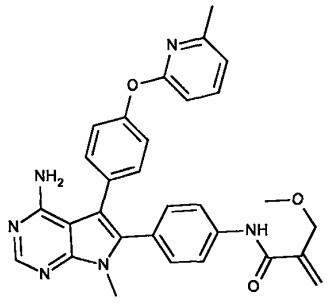
[0496]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
387		B	A
388		C	B
389		B	
390		D	
391		A	A

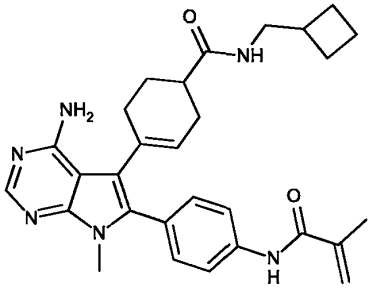
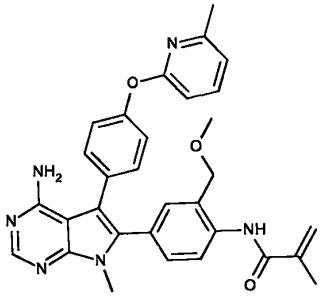
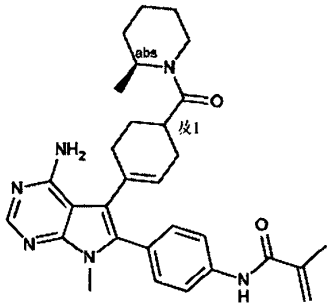
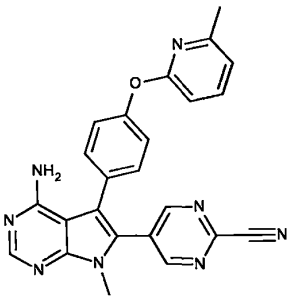
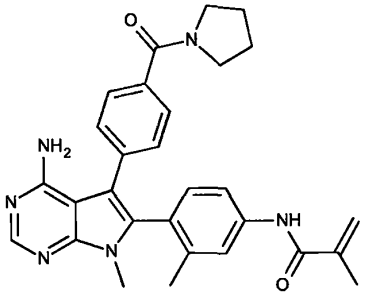
[0497]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
392		D	
393		D	C
394		C	
395		A	A
396		B	

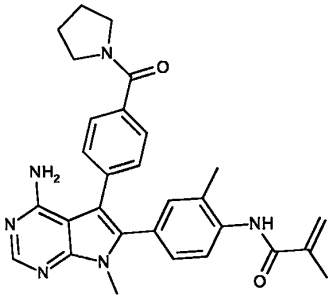
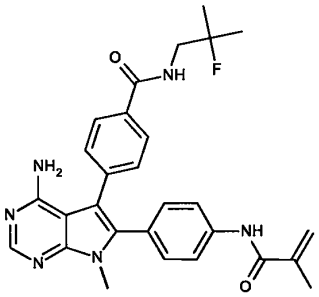
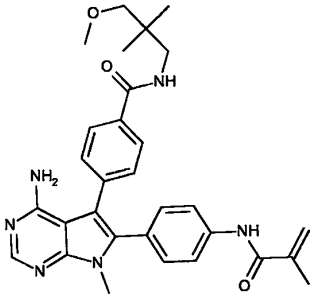
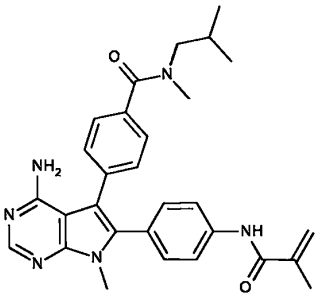
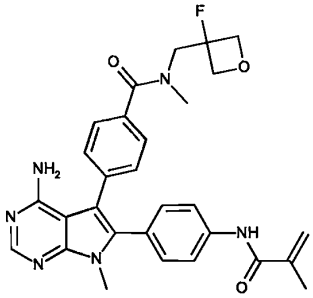
[0498]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
397		D	C
398		A	A
399		B	A
400		B	
401		A	A

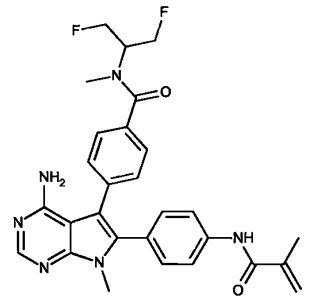
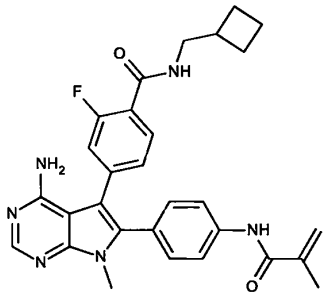
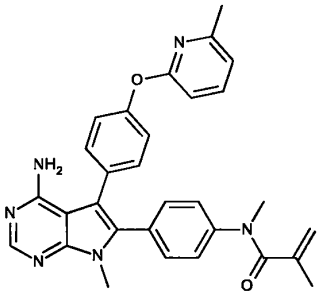
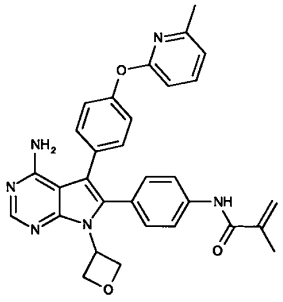
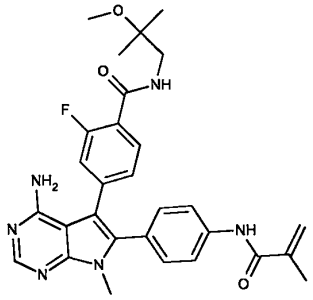
[0499]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
402		B	
403		B	
404		B	
405		A	
406		A	A

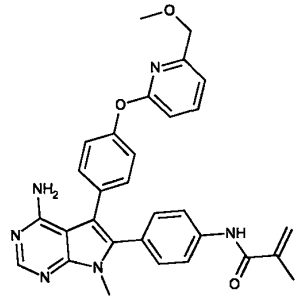
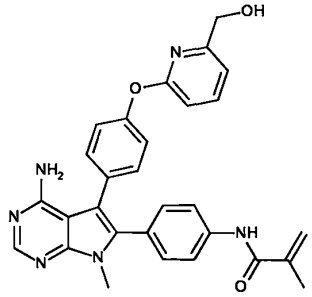
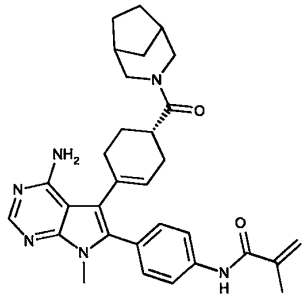
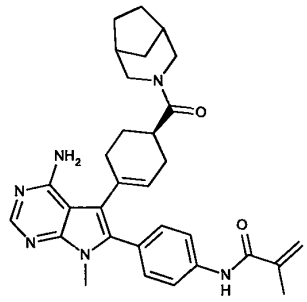
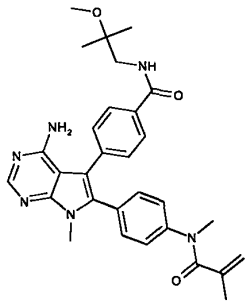
[0500]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
407		D	
408		A	A
409		A	A
410		A	A
411		C	C

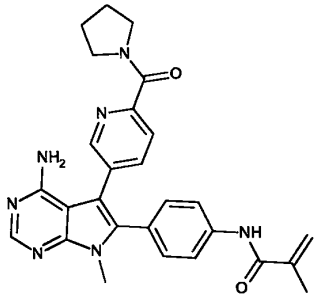
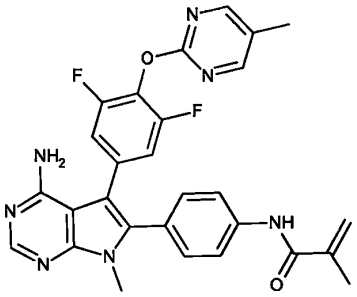
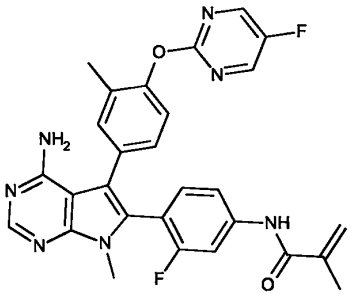
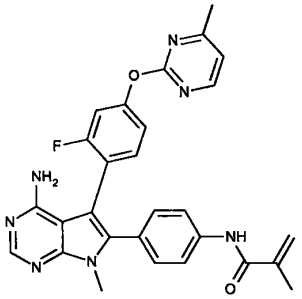
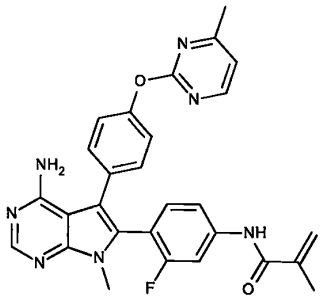
[0501]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
412		A	
413		A	A
414		B	
415		A	A
416		A	A

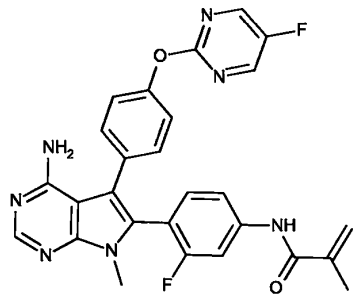
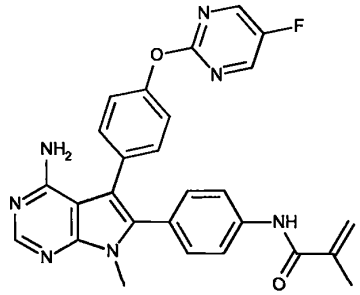
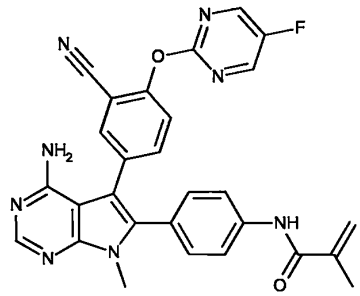
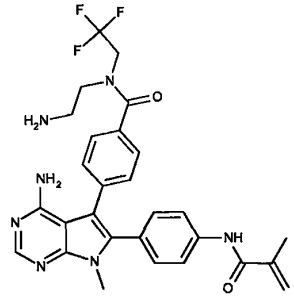
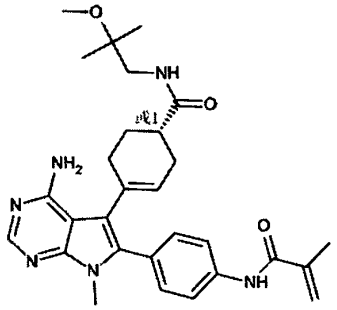
[0502]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
417		A	A
418		A	A
419		A	A
420		D	
421		D	

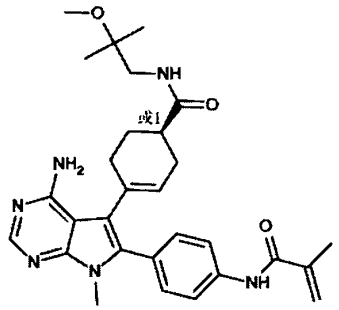
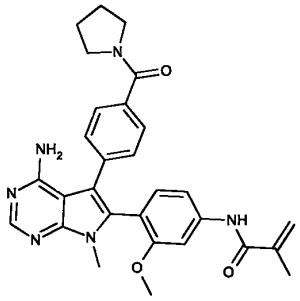
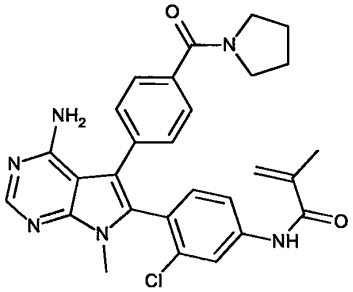
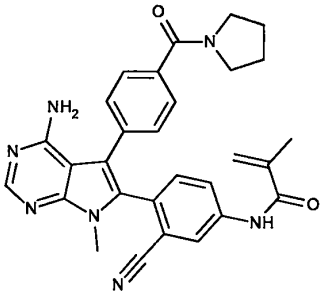
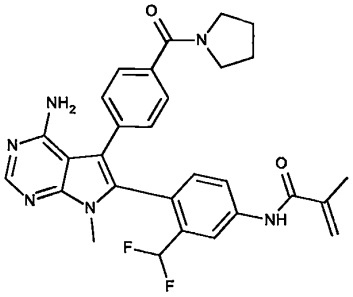
[0503]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
422		D	
423		A	B
424		A	A
425		A	A
426		A	A

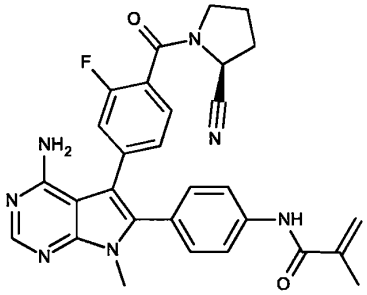
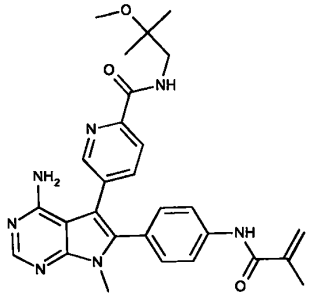
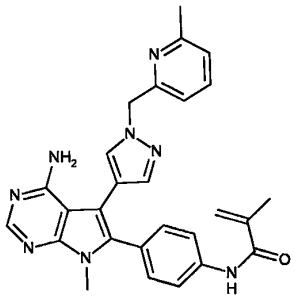
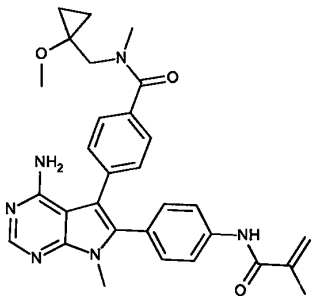
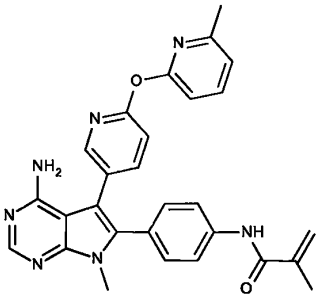
[0504]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
427		A	A
428		A	A
429		B	B
430		C	
431		C	

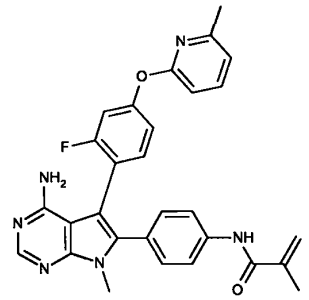
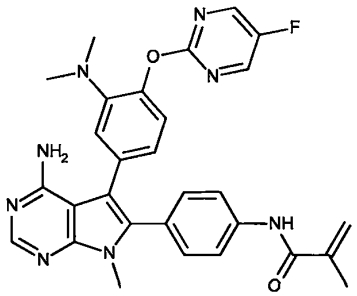
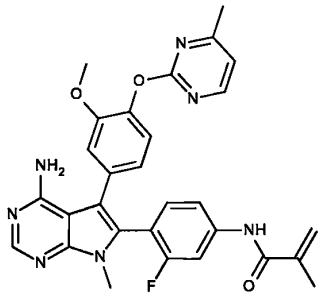
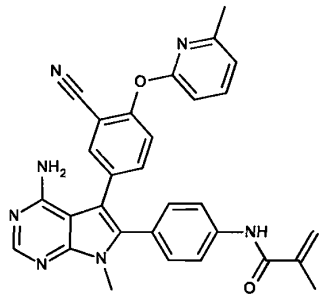
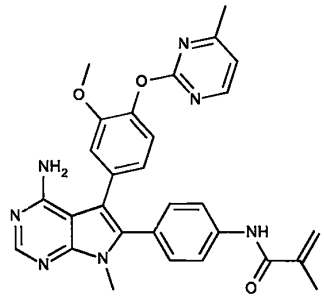
[0505]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
432		D	
433		A	A
434		A	A
435		A	B
436		A	B

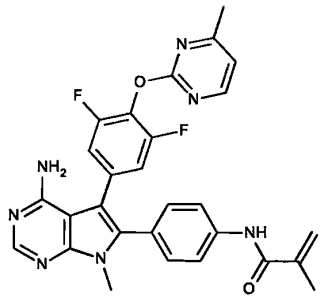
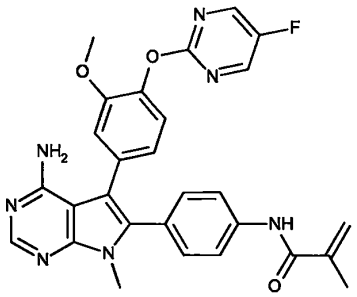
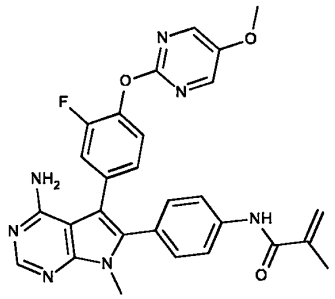
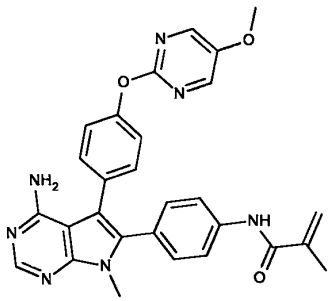
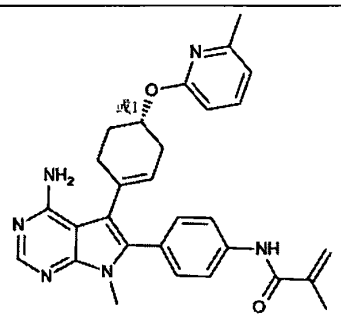
[0506]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
437		A	A
438		D	
439		D	
440		D	
441		C	C

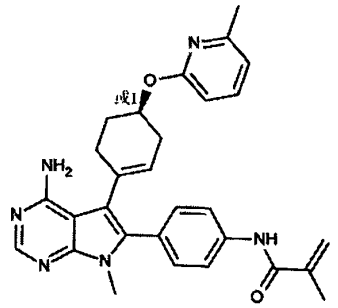
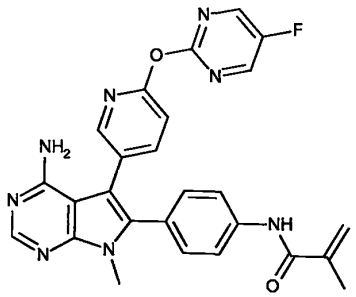
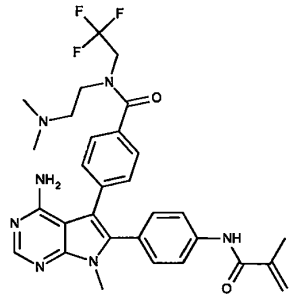
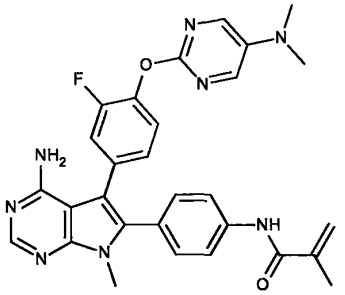
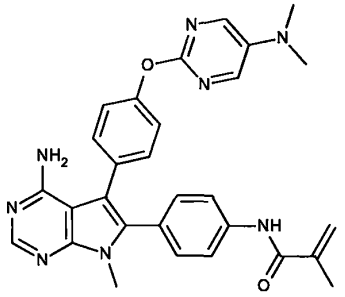
[0507]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
442		A	A
443		D	
444		A	A
445		A	A
446		B	A

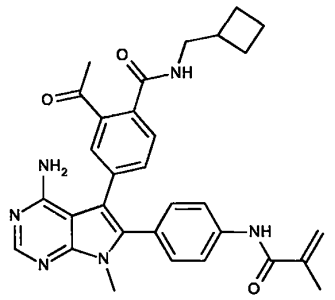
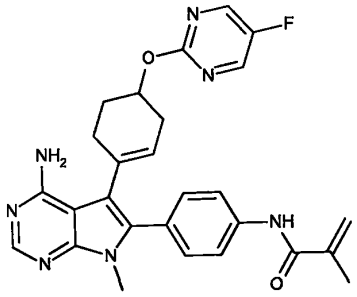
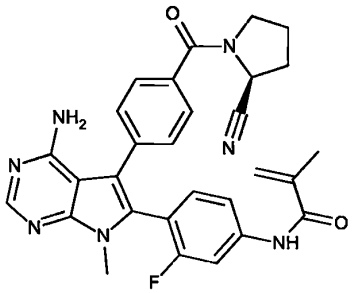
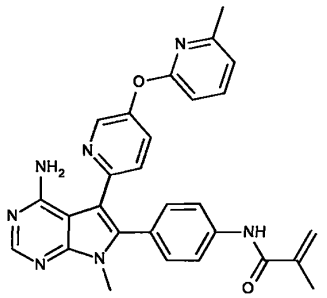
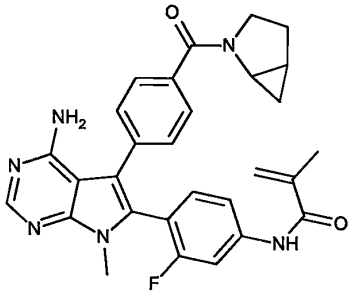
[0508]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
447		A	A
448		C	B
449		C	B
450		C	
451		C	A

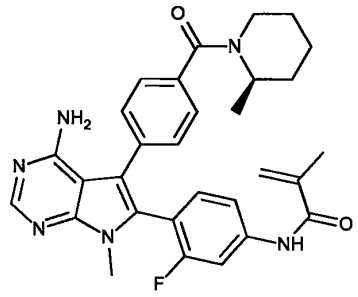
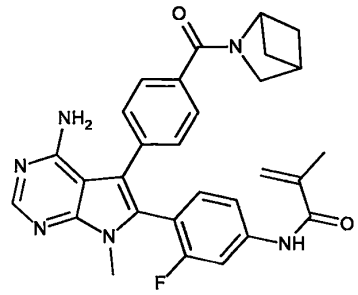
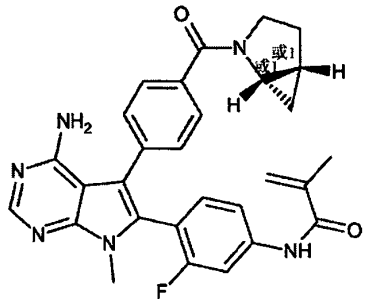
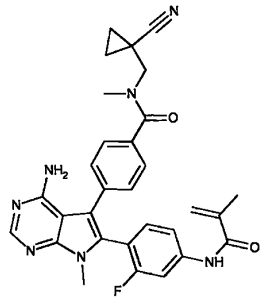
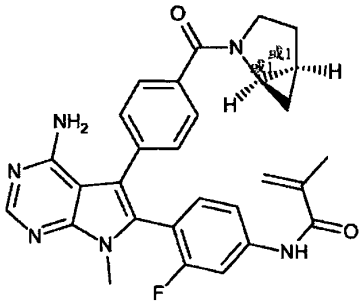
[0509]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
452		D	C
453		D	
454		C	
455		C	
456		C	

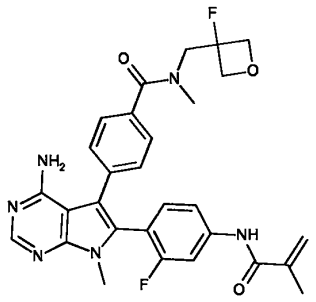
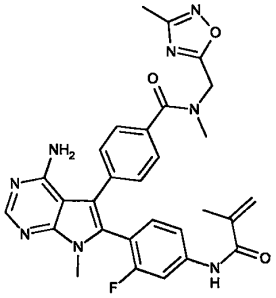
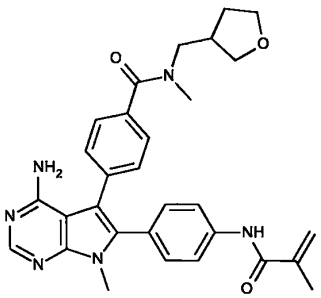
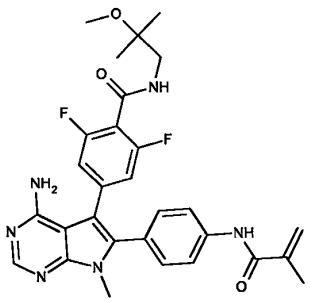
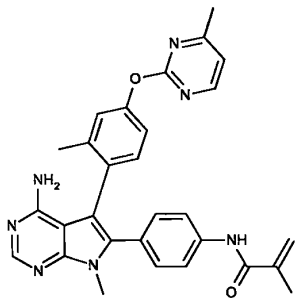
[0510]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
457		B	
458		B	A
459		A	A
460		A	A
461		A	A

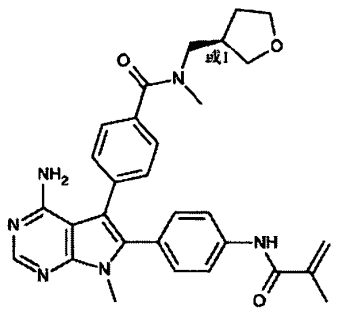
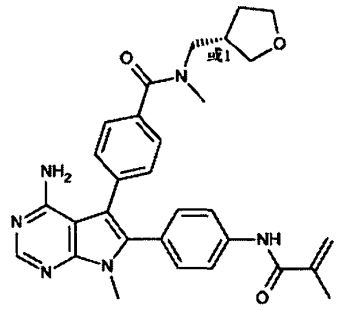
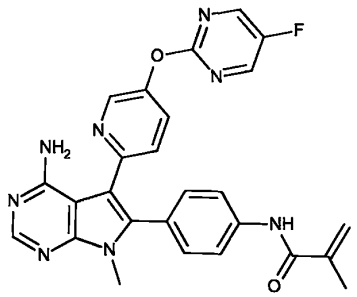
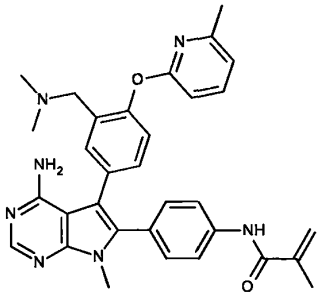
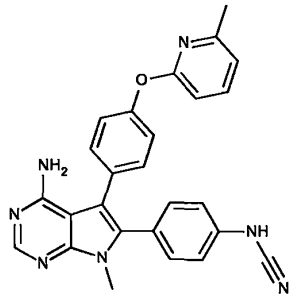
[0511]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
462		A	A
463		A	A
464		A	A
465		A	A
466		A	A

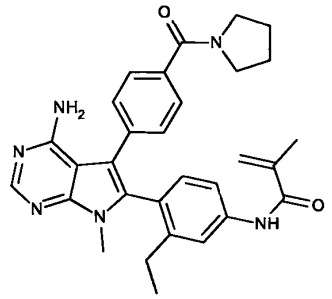
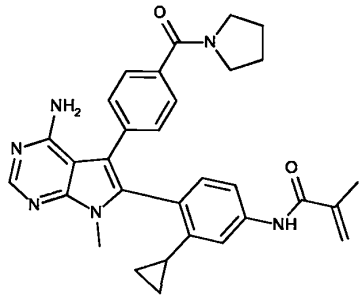
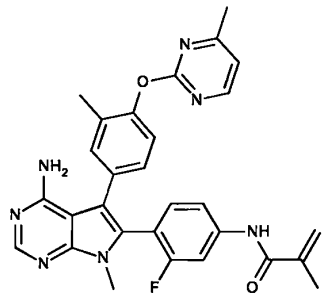
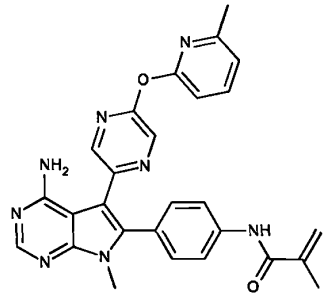
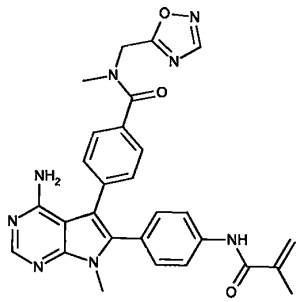
[0512]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
467		B	
468		A	A
469		C	
470		B	
471		B	B

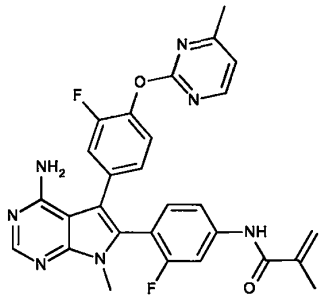
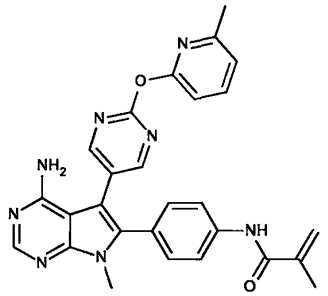
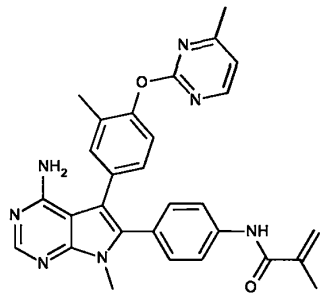
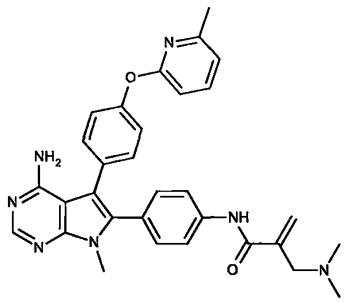
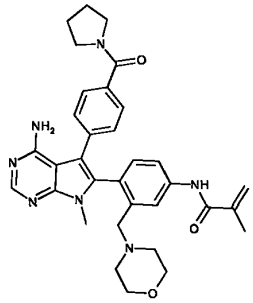
[0513]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
472		C	
473		C	
474		A	A
475		D	C
476		A	A

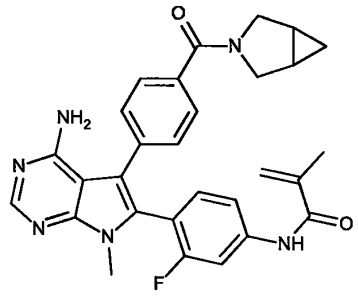
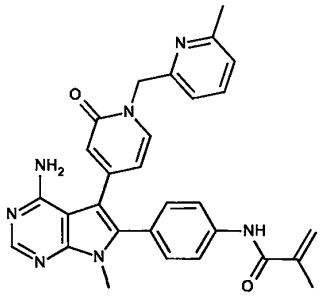
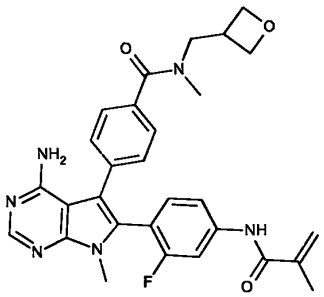
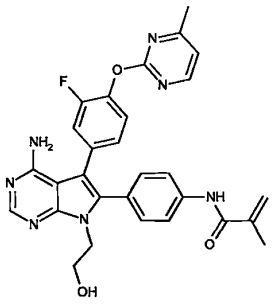
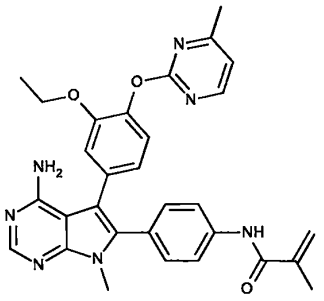
[0514]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
477		B	
478		B	
479		A	A
480		C	
481		D	

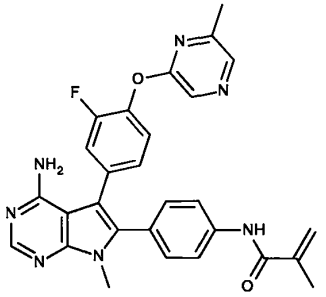
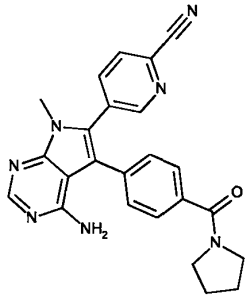
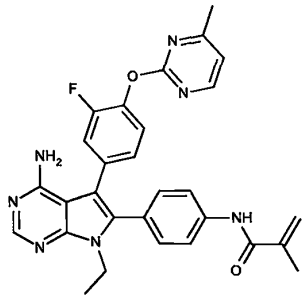
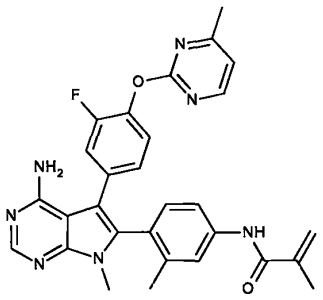
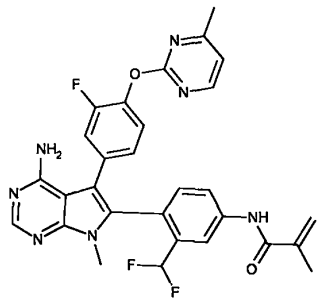
[0515]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
482		A	A
483		D	
484		A	A
485		A	A
486		D	

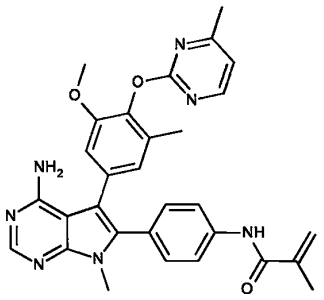
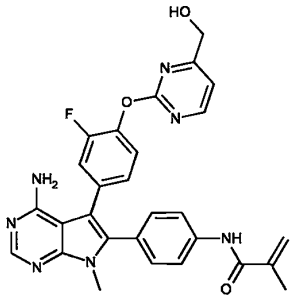
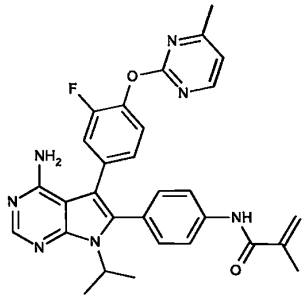
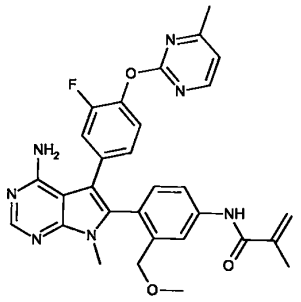
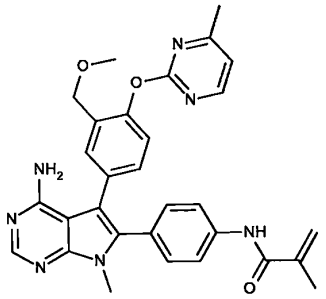
[0516]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
487		A	A
488		D	
489		C	
490		A	A
491		D	

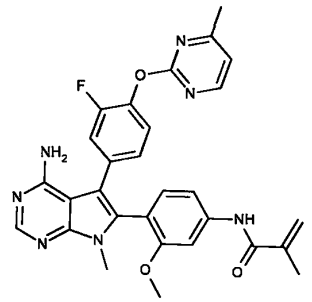
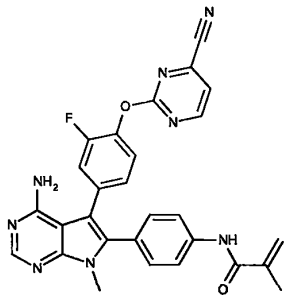
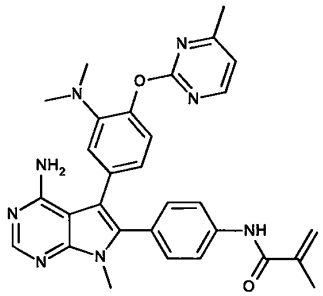
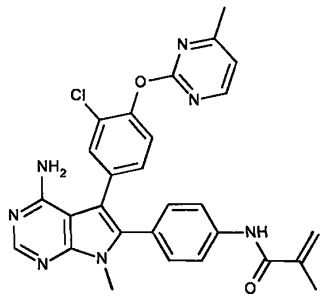
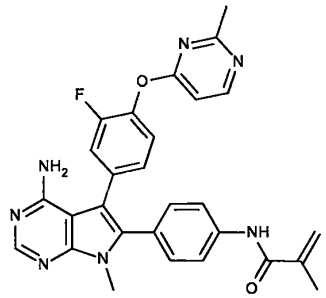
[0517]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
492		A	A
493		D	
494		A	A
495		A	A
496		A	A

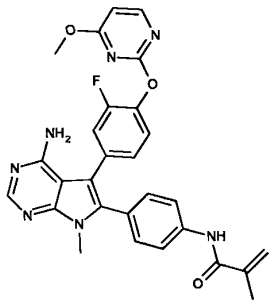
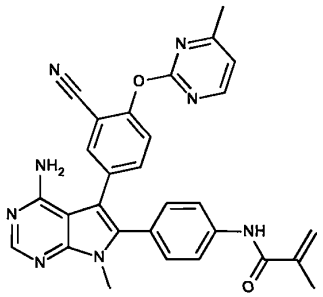
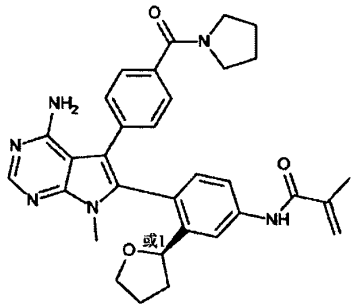
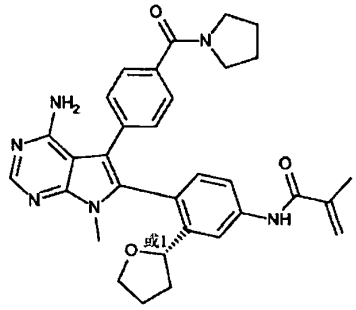
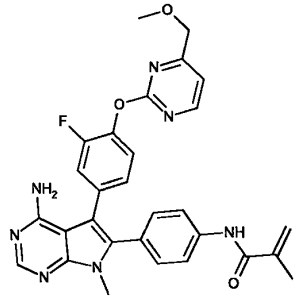
[0518]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
497		B	A
498		A	A
499		A	A
500		A	A
501		D	

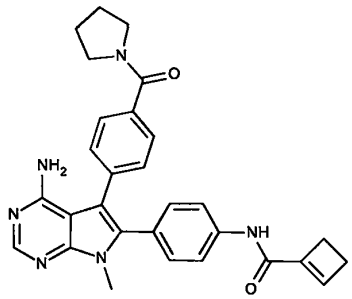
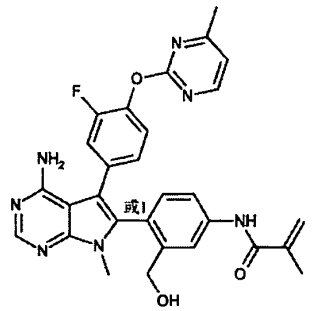
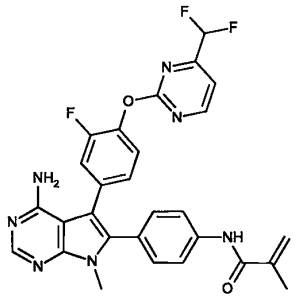
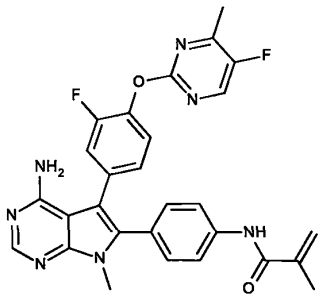
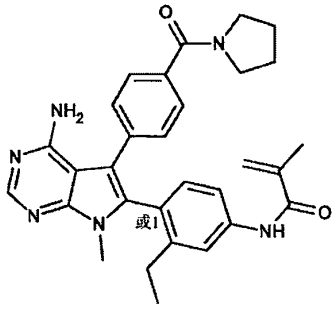
[0519]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
502		A	A
503		A	A
504		D	
505		A	A
506		C	C

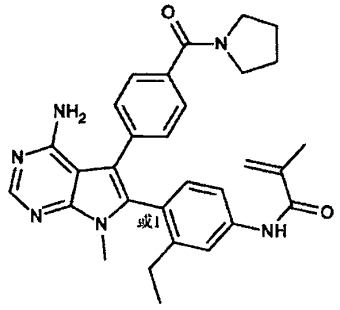
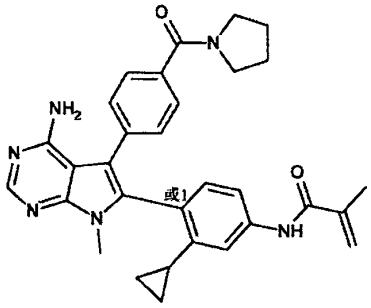
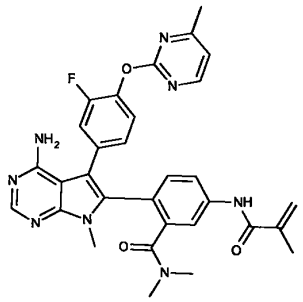
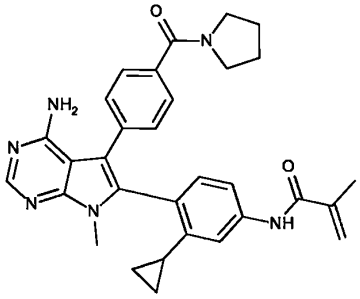
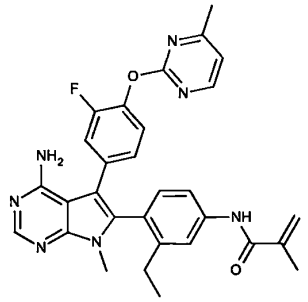
[0520]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
507		A	A
508		A	A
509		C	
510		A	
511		A	A

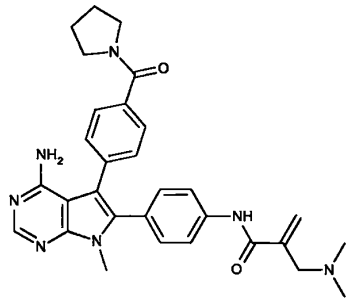
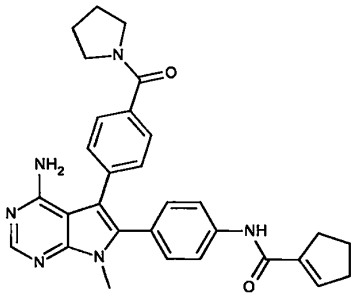
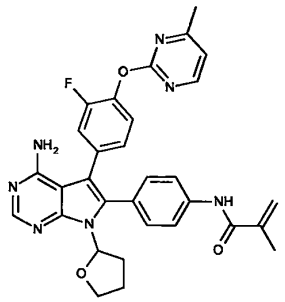
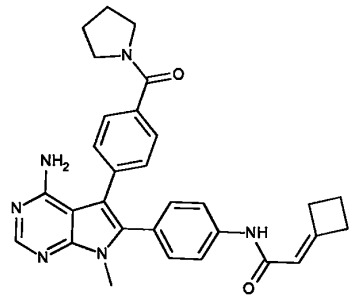
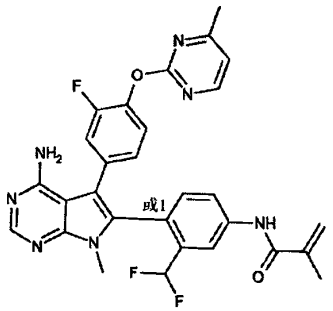
[0521]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
512		A	A
513		A	A
514		A	A
515		A	A
516		A	

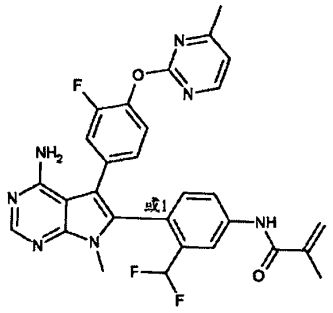
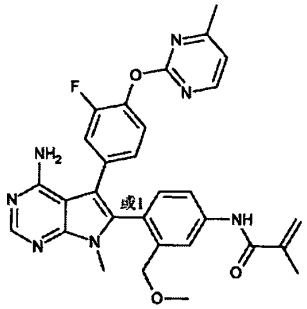
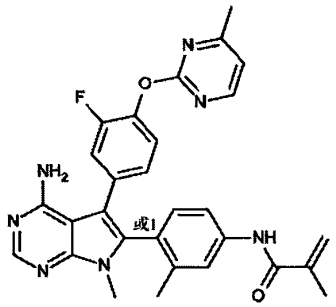
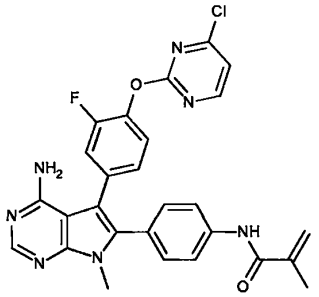
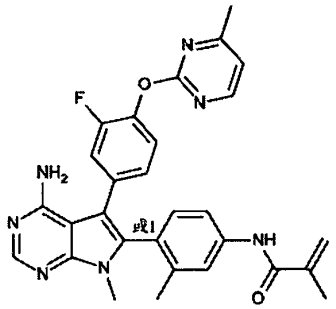
[0522]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
517		C	
518		A	
519		D	
520		B	B
521		A	A

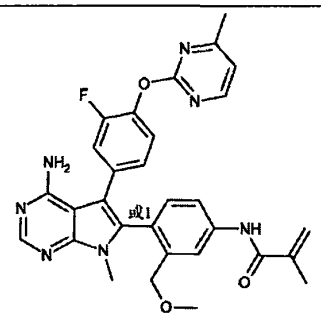
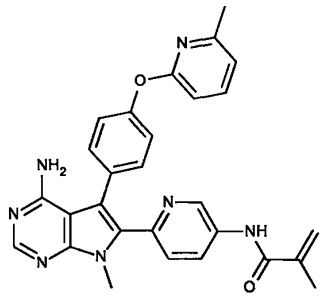
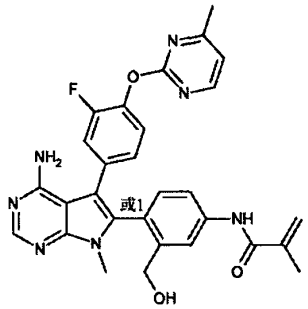
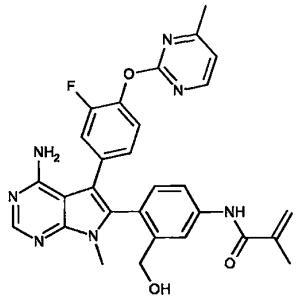
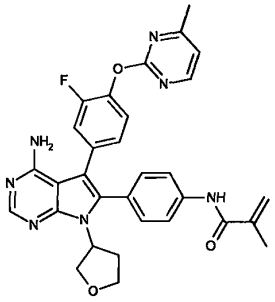
[0523]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
522		A	A
523		D	
524		A	A
525		D	
526		A	A

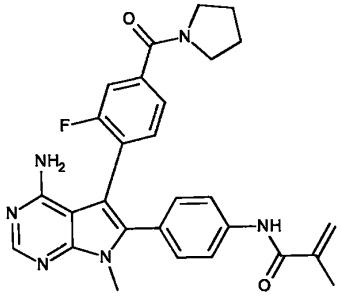
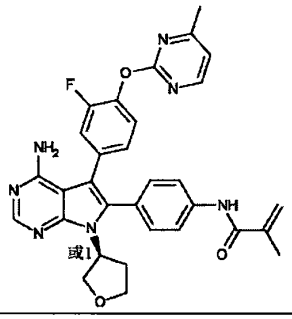
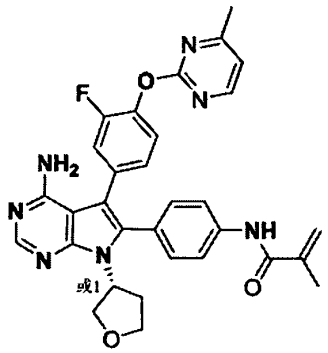
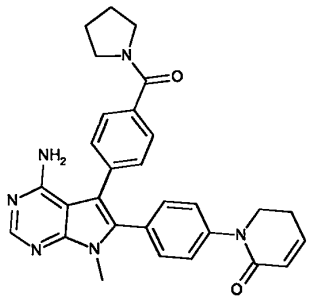
[0524]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
527		A	A
528		A	
529		A	A
530		A	A
531		A	A

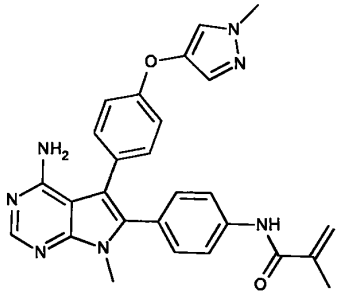
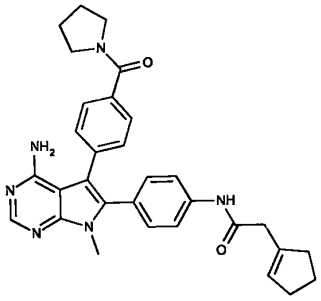
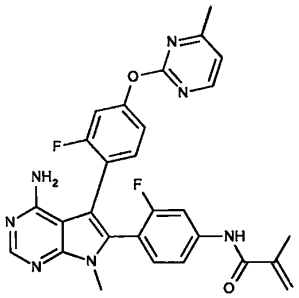
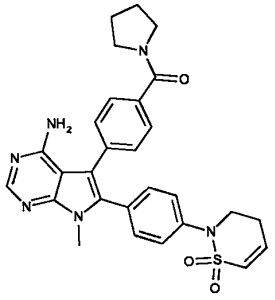
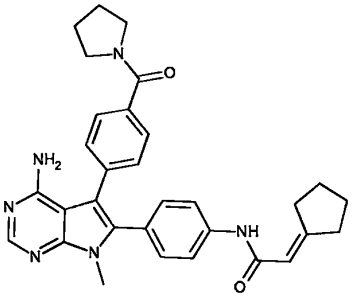
[0525]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
532		A	
533		A	A
534		A	
535		A	A
536		A	

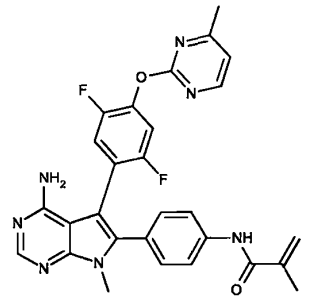
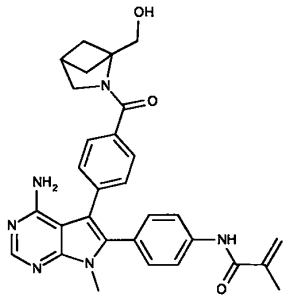
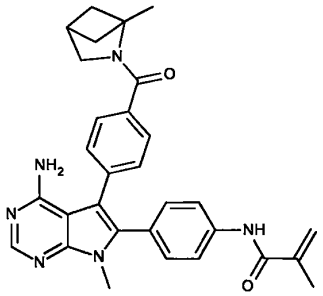
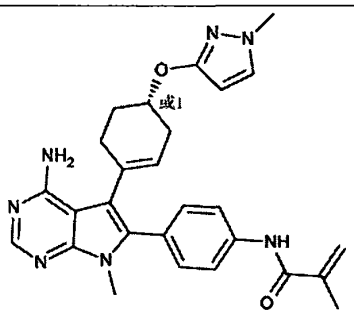
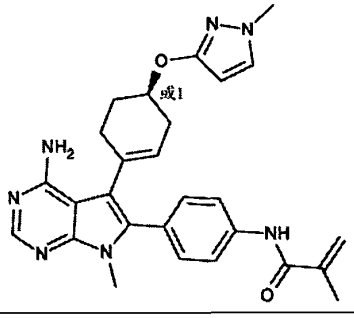
[0526]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
537		B	A
538		A	A
539		A	A
540		D	

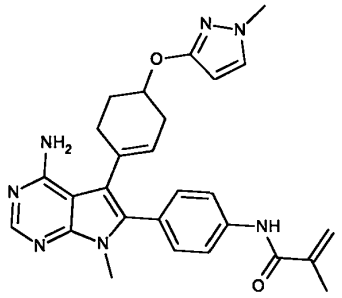
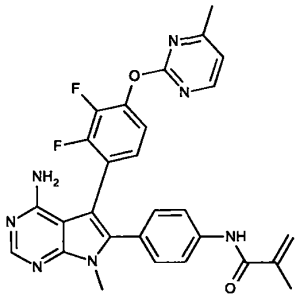
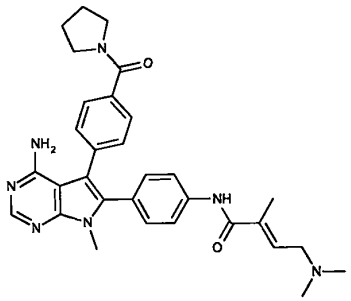
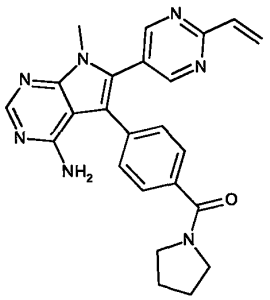
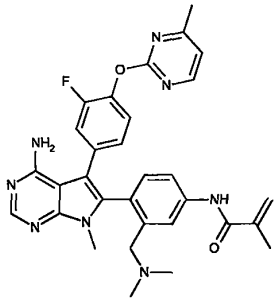
[0527]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
541		D	C
542		D	
543		A	A
544		D	
545		D	

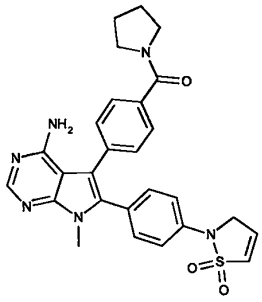
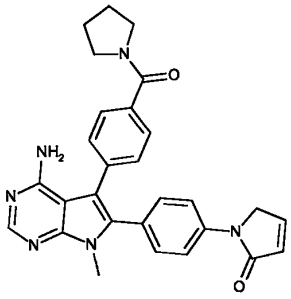
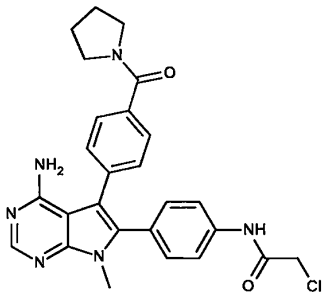
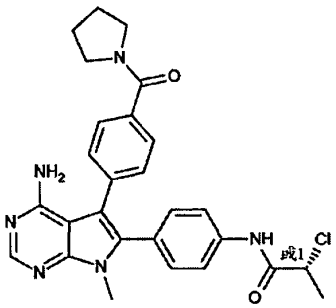
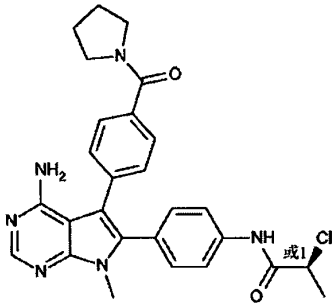
[0528]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
546		A	A
547		C	
548		A	
549		D	
550		B	A

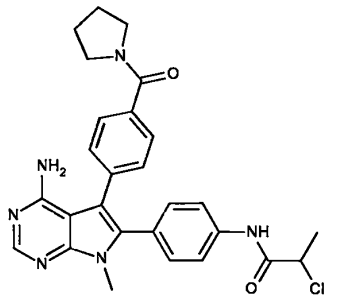
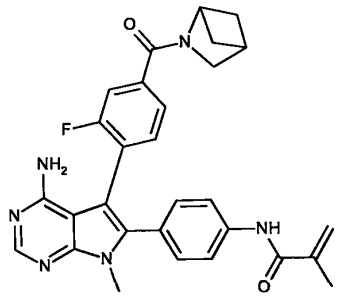
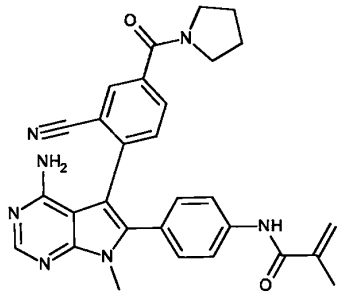
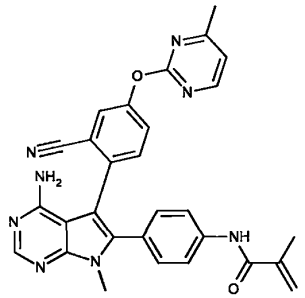
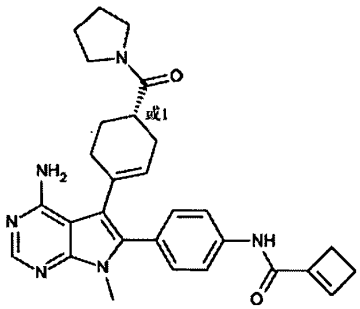
[0529]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
551		C	
552		A	A
553		C	
554		C	C
555		A	

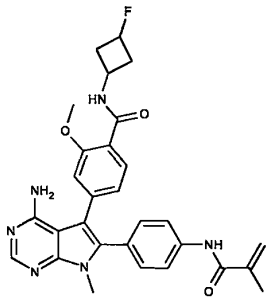
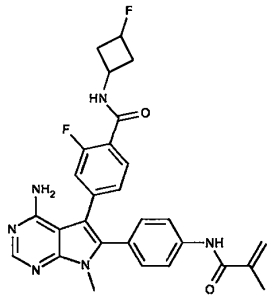
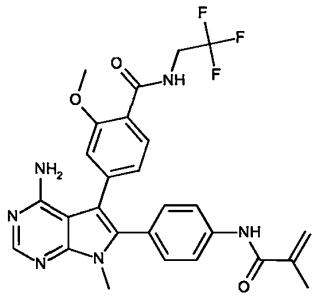
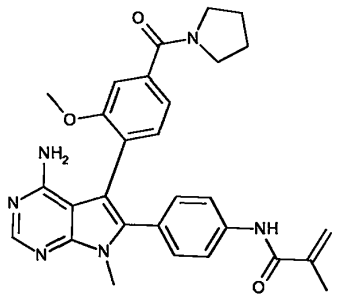
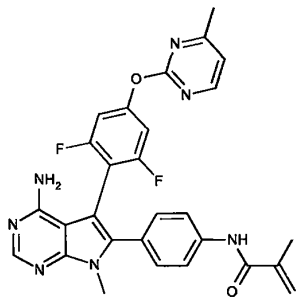
[0530]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
556		C	
557		D	
558		A	A
559		C	C
560		B	B

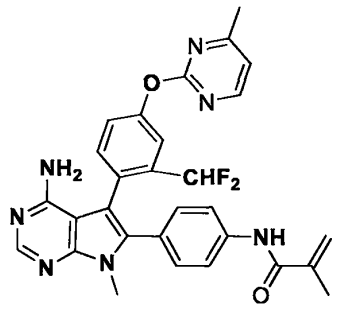
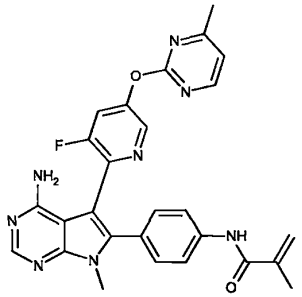
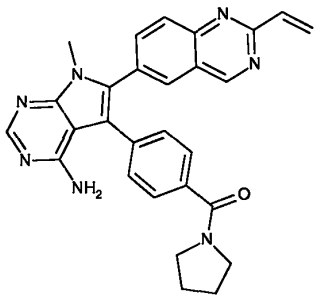
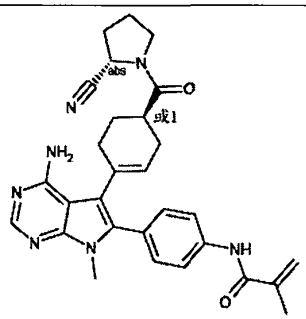
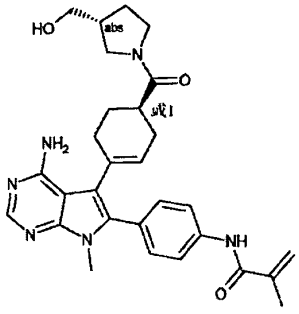
[0531]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
561		C	
562		B	A
563		D	C
564		D	C
565		A	A

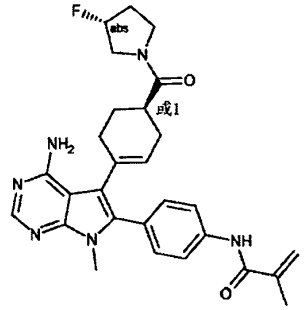
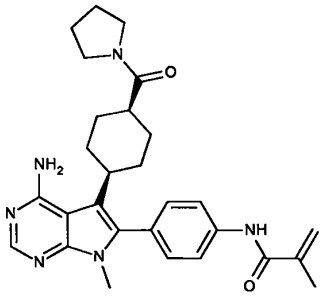
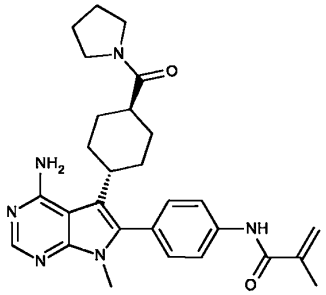
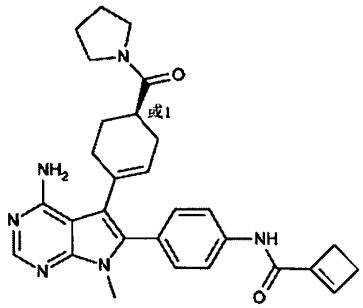
[0532]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
566		A	A
567		B	A
568		A	A
569		B	B
570		A	A

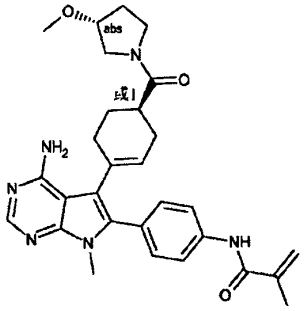
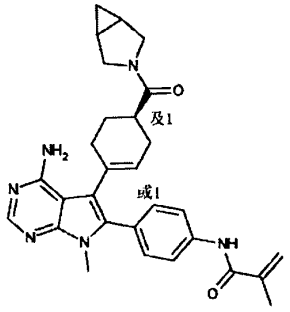
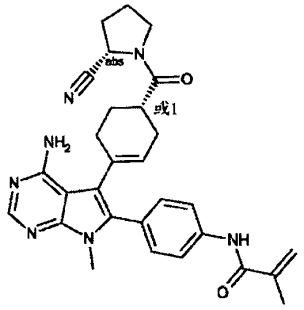
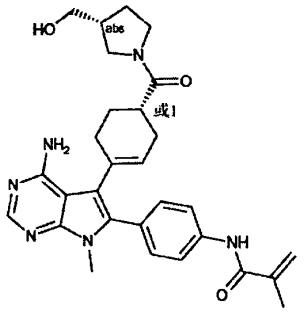
[0533]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
571		D	C
572		A	A
573		D	C
574		C	
575		D	

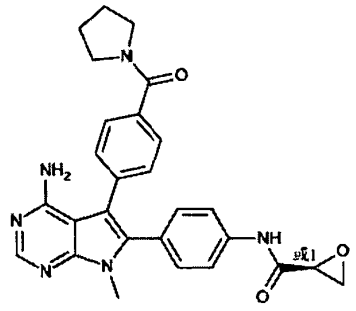
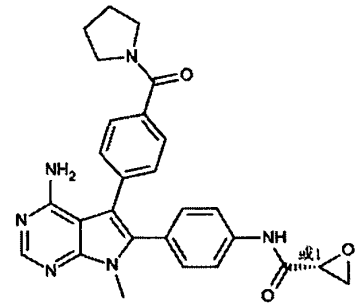
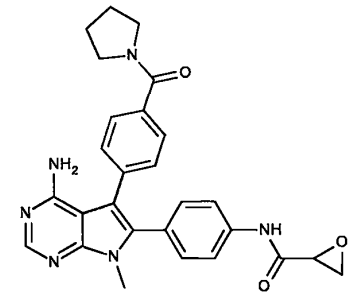
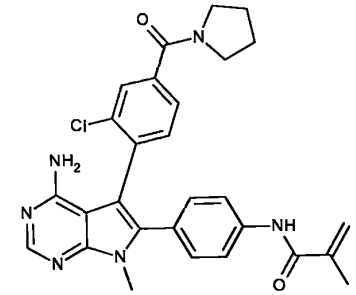
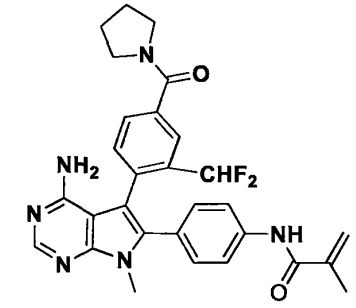
[0534]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
576		D	
577		D	
578		D	
579		C	

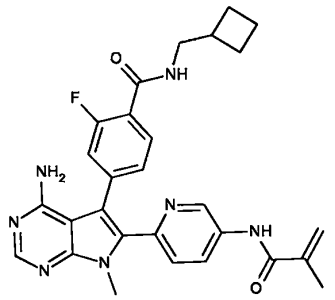
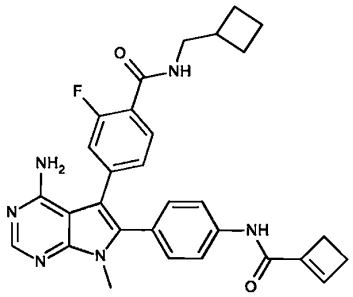
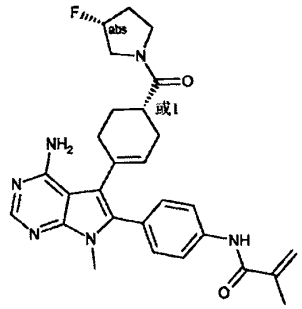
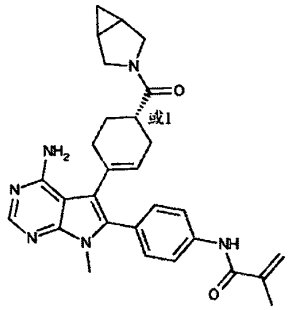
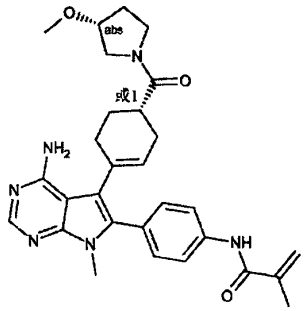
[0535]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
580		D	
581		D	
582		A	A
583		C	

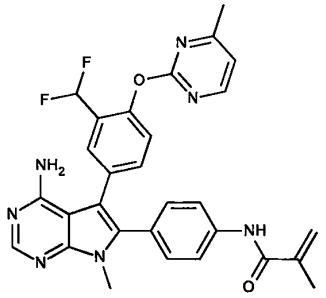
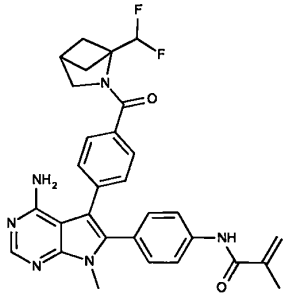
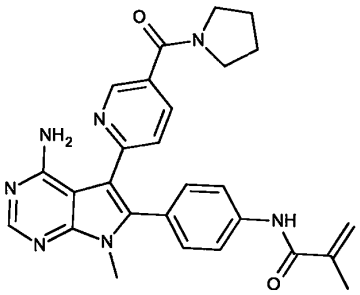
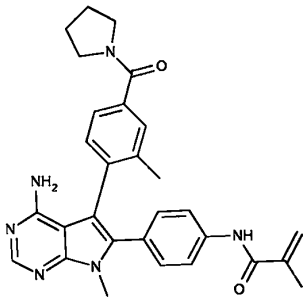
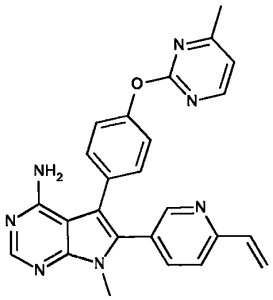
[0536]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
584		B	C
585		B	
586		B	
587		D	
588		D	

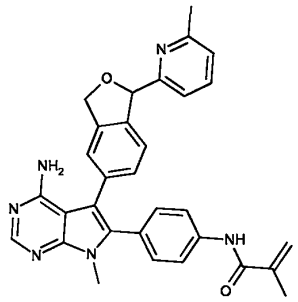
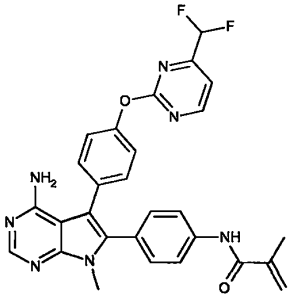
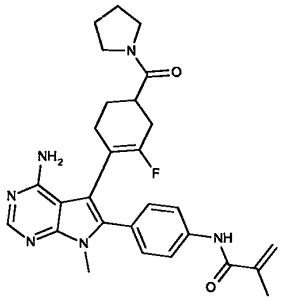
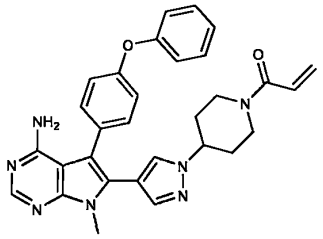
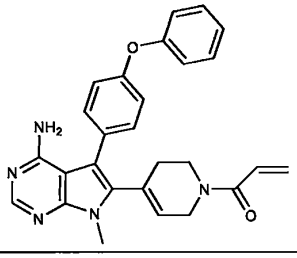
[0537]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
589		A	A
590		A	A
591		B	
592		A	A
593		C	

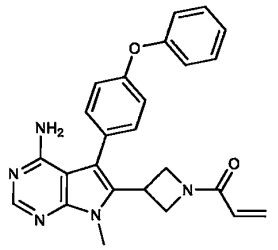
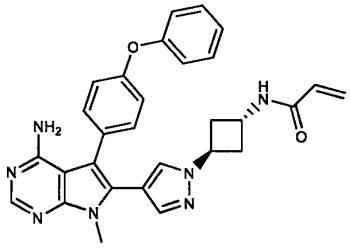
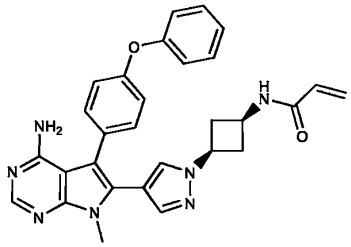
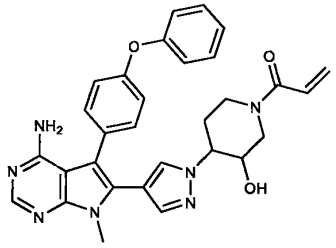
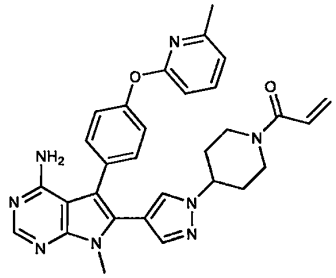
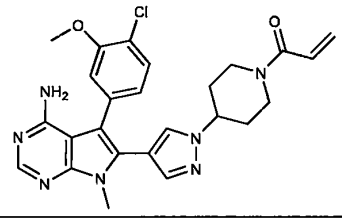
[0538]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
594		B	A
595		A	
596		A	
597		D	
598		B	C

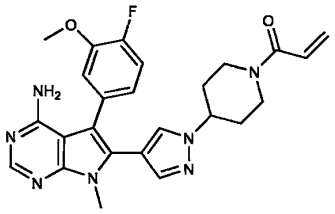
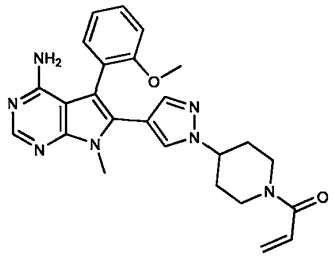
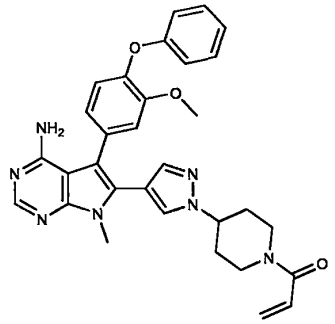
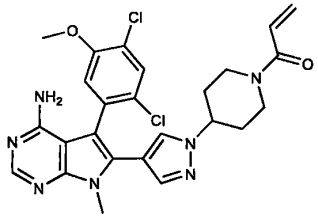
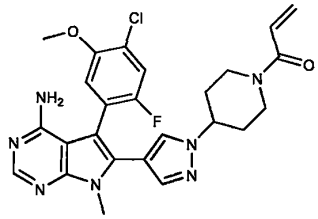
[0539]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
599		B	
600		A	A
601		D	C
602		A	A
603		A	A

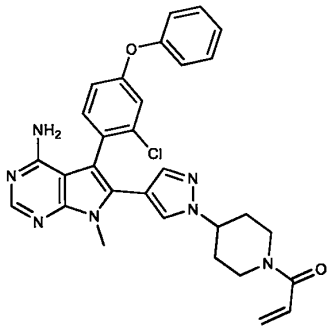
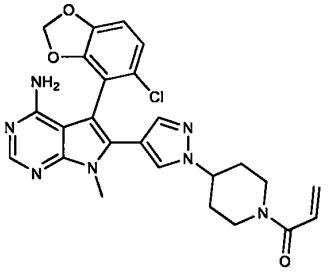
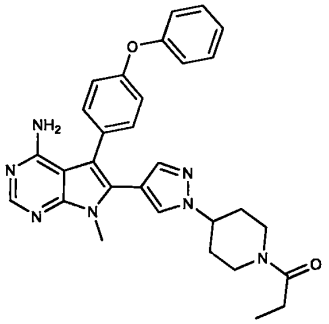
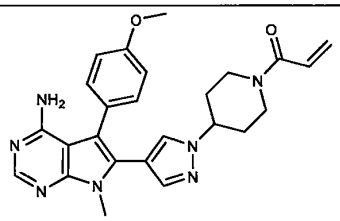
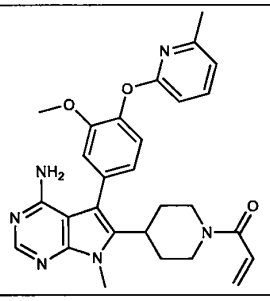
[0540]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
604		A	
605		A	
606		A	
607		A	A
608		A	A
609		C	

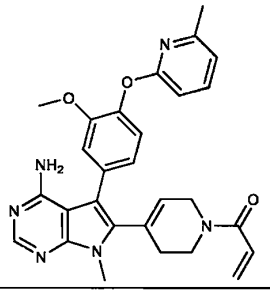
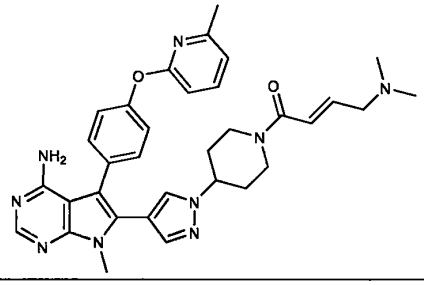
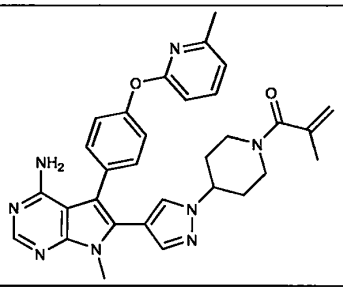
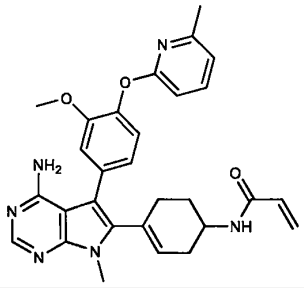
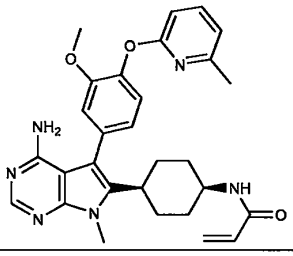
[0541]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
610		C	
611		D	
612		B	
613		D	
614		D	

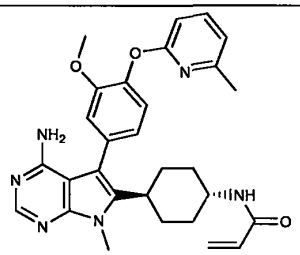
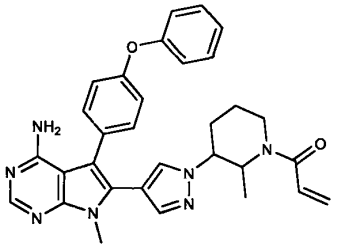
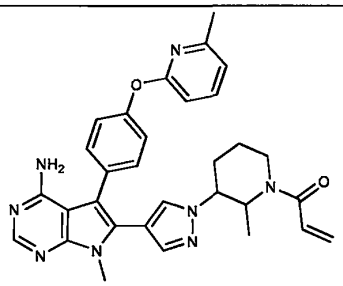
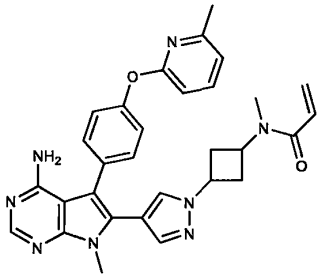
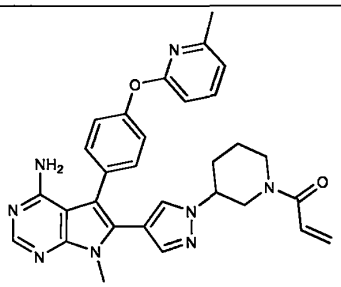
[0542]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
615		A	
616		D	
617		B	C
618		A	A
619		B	B

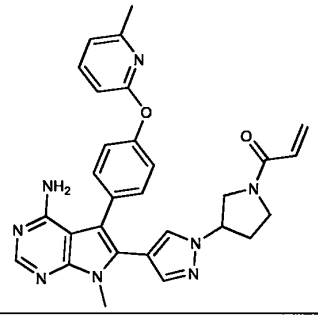
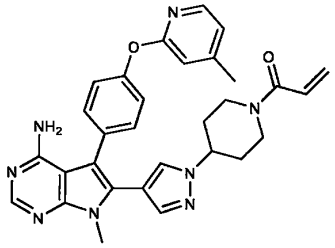
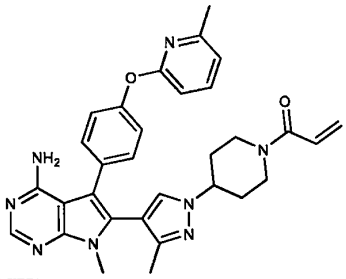
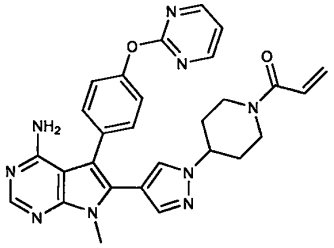
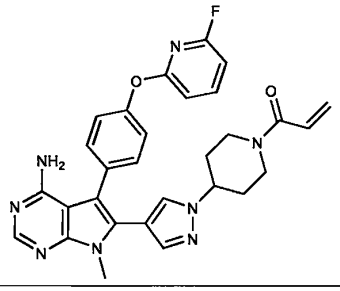
[0543]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
620		A	A
621		A	A
622		C	D
623		B	B
624		D	

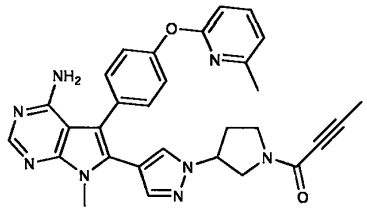
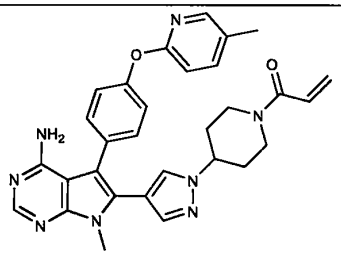
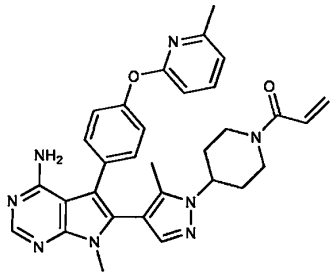
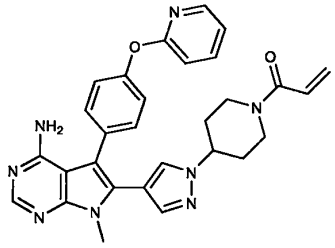
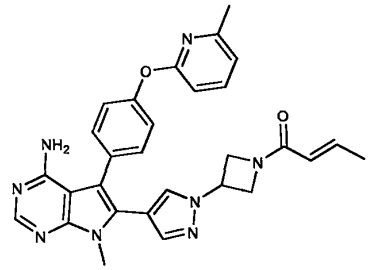
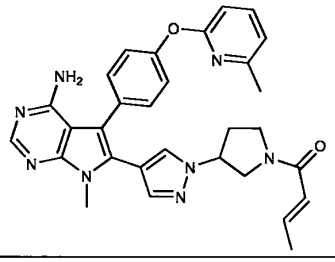
[0544]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
625		C	
626		B	C
627		A	A
628		A	A
629		A	A

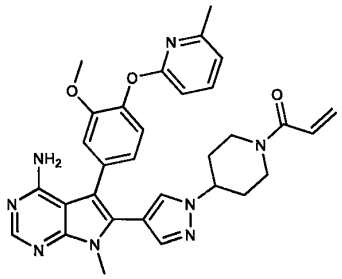
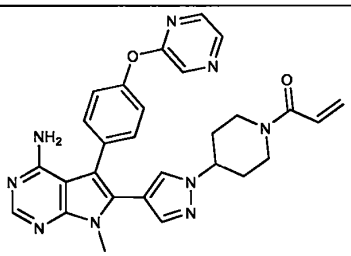
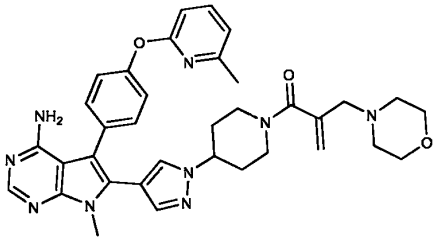
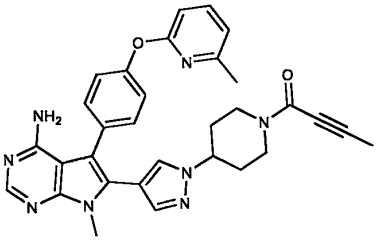
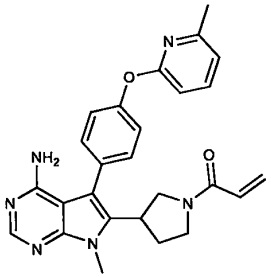
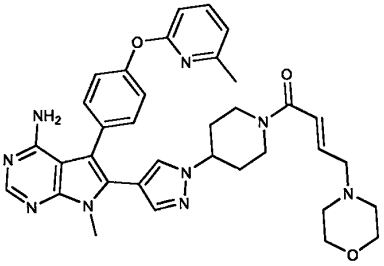
[0545]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
630		A	A
631		B	B
632		A	A
633		B	B
634		A	A

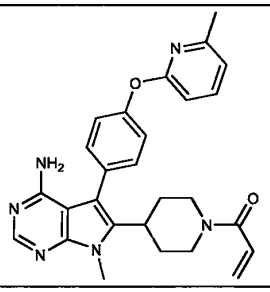
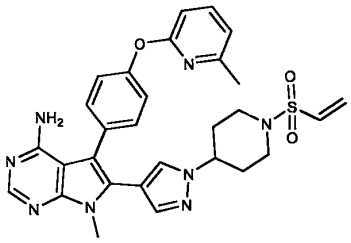
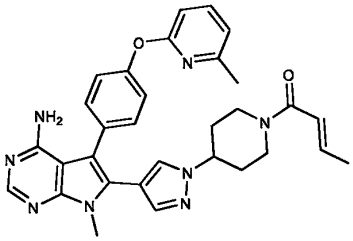
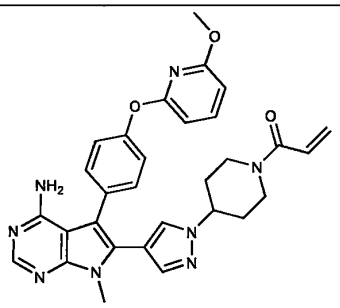
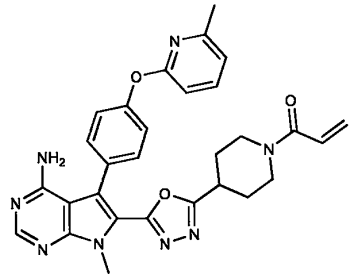
[0546]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
635		B	A
636		B	A
637		A	A
638		A	A
639		A	A
640		A	A

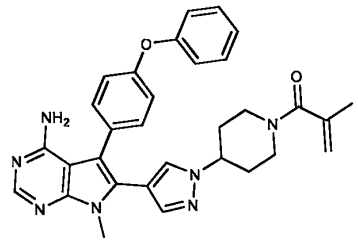
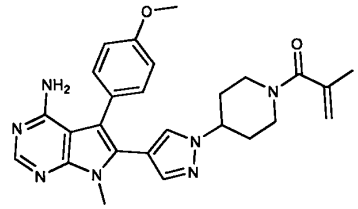
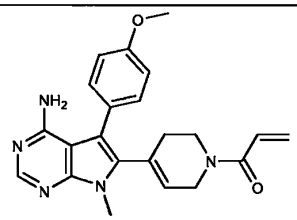
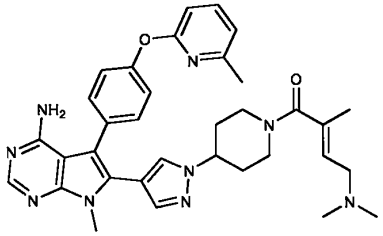
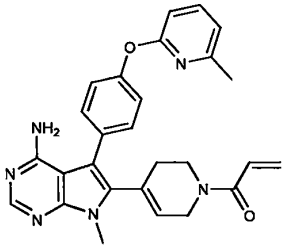
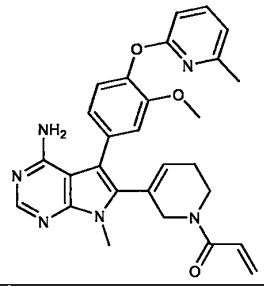
[0547]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
641		A	A
642		C	B
643		C	C
644		C	C
645		A	A
646		B	B

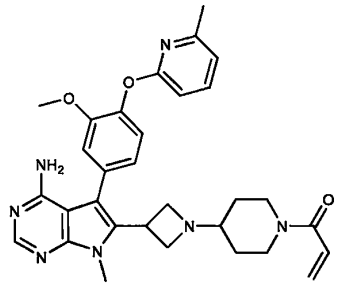
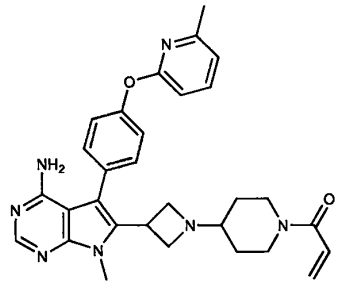
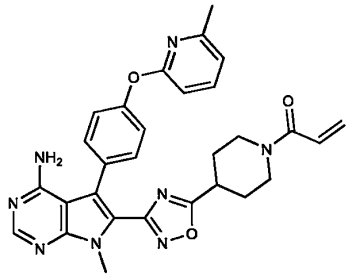
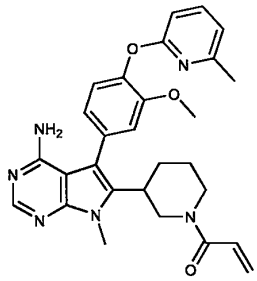
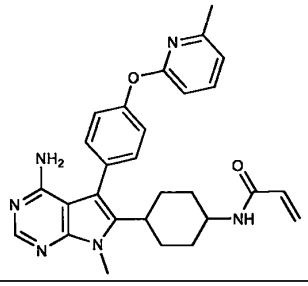
[0548]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
647		A	A
648		A	B
649		B	C
650		A	A
651		B	A

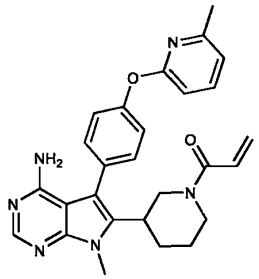
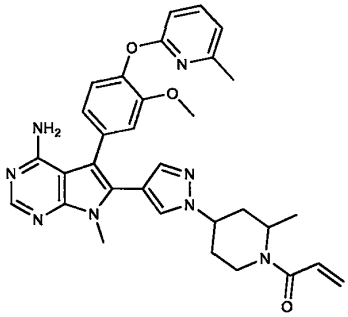
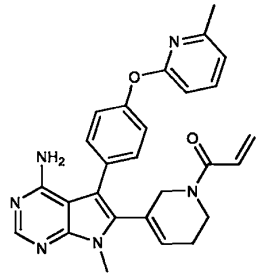
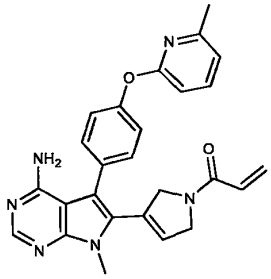
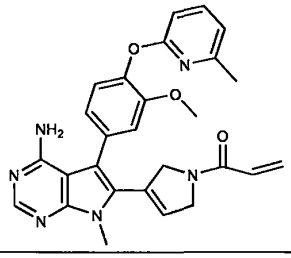
[0549]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
652		B	D
653		C	D
654		A	A
655		C	D
656		A	A
657		D	D

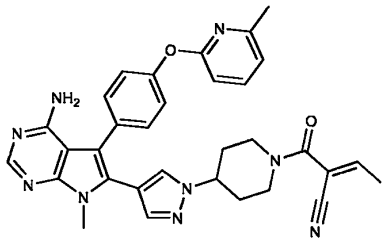
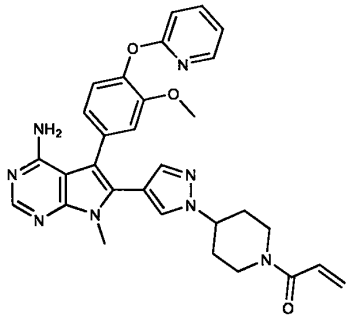
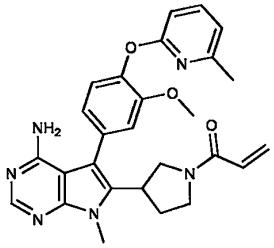
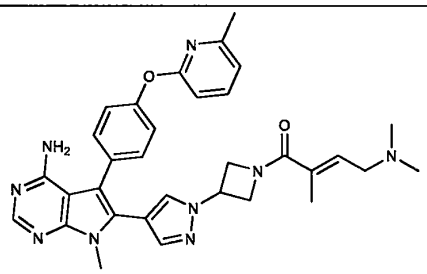
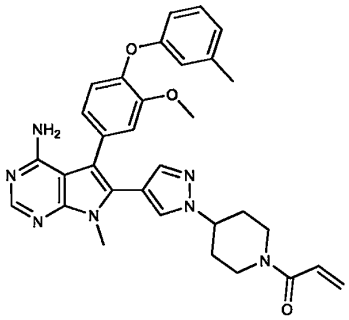
[0550]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
658		D	
659		D	
660		A	A
661		D	D
662		B	C

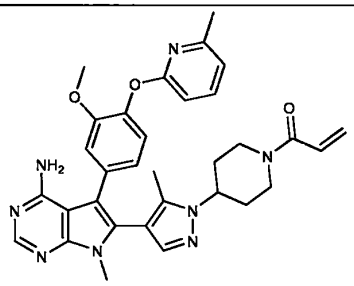
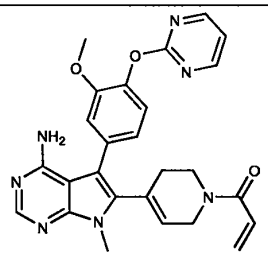
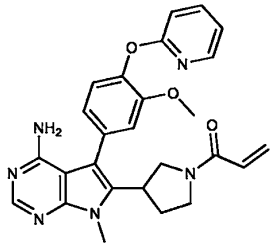
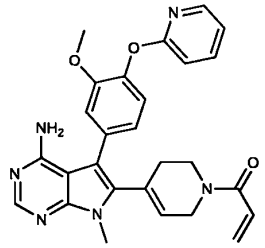
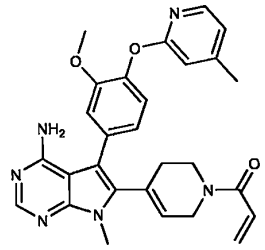
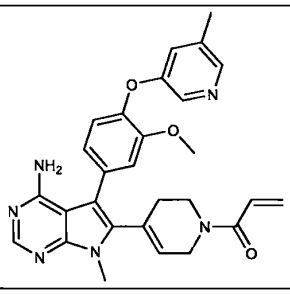
[0551]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
663		C	C
664		B	B
665		B	C
666		A	A
667		B	B

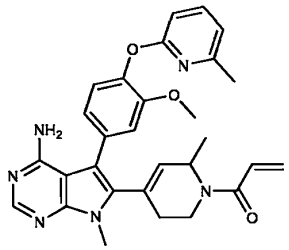
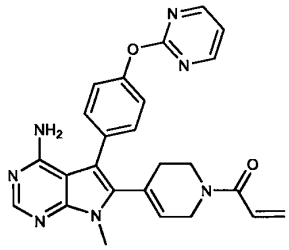
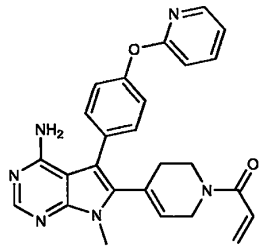
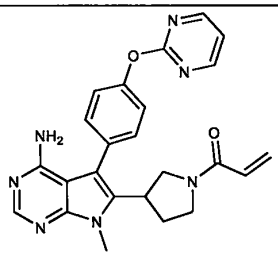
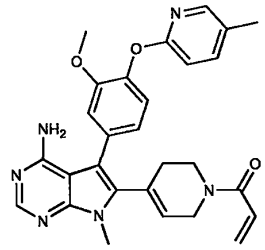
[0552]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
668		A	D
669		C	C
670		C	C
671		C	D
672		B	C

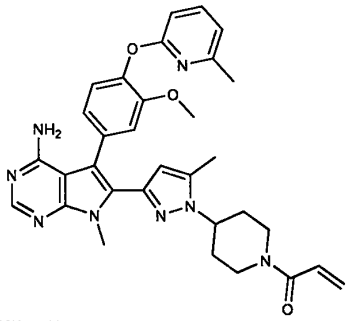
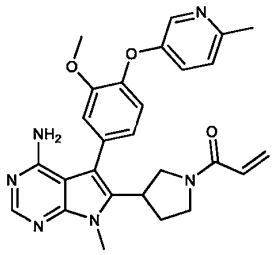
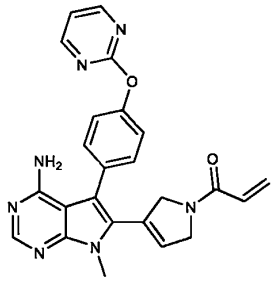
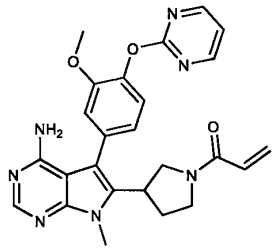
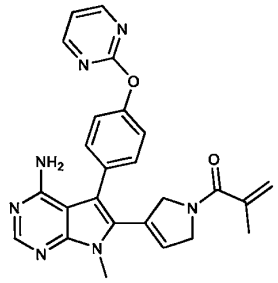
[0553]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
673		A	A
674		A	A
675		C	D
676		A	A
677		A	A
678		A	B

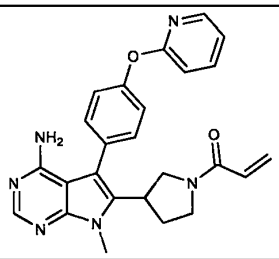
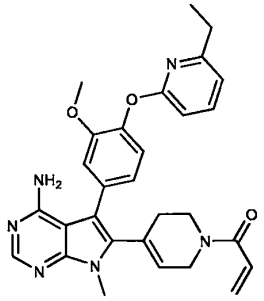
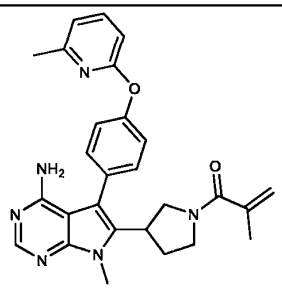
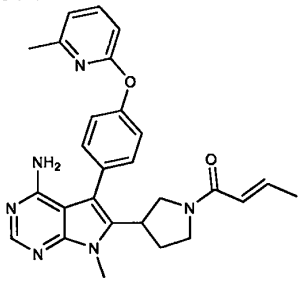
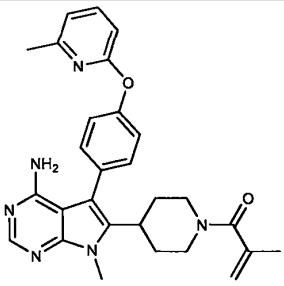
[0554]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
679		A	
680		A	A
681		A	A
682		B	A
683		A	A

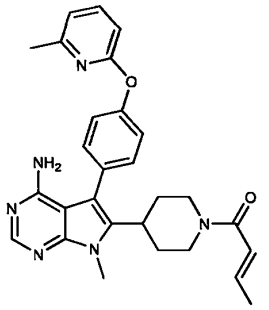
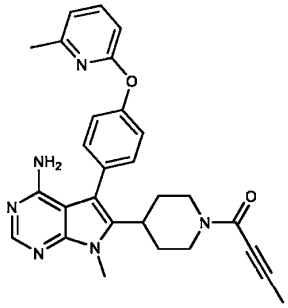
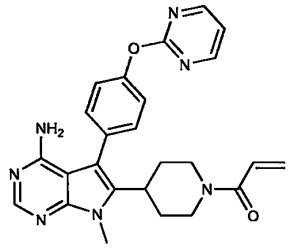
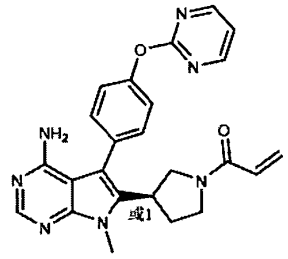
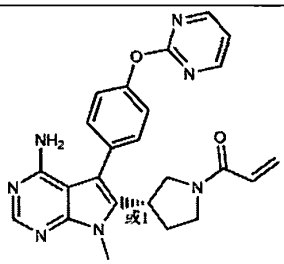
[0555]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
684		D	D
685		D	D
686		A	A
687		D	D
688		D	D

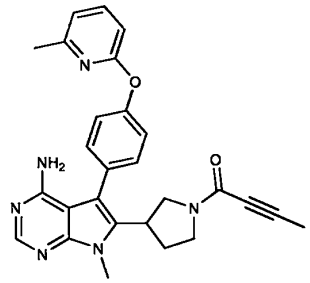
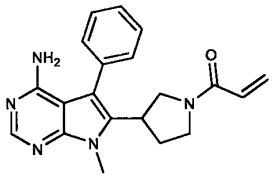
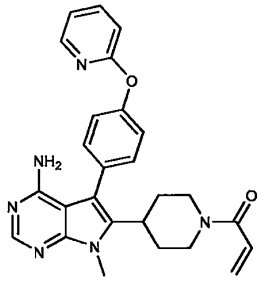
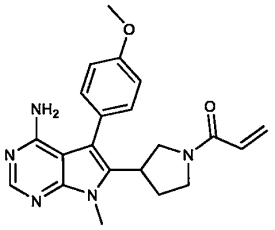
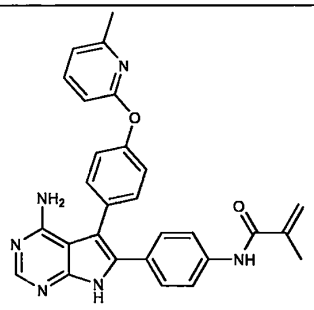
[0556]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
689		A	A
690		A	A
691		C	D
692		D	D
693		C	D

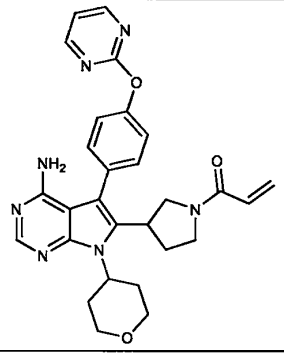
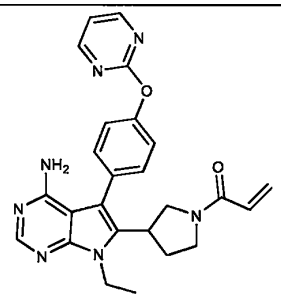
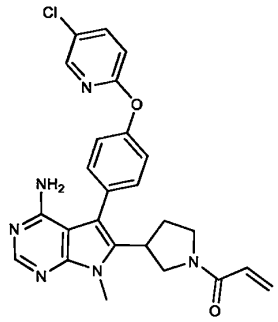
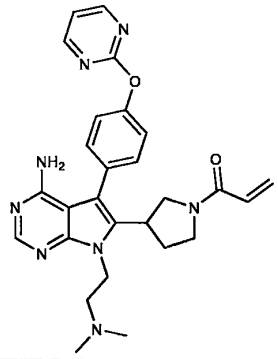
[0557]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
694		C	C
695		B	A
696		C	B
697		A	A
698		C	B

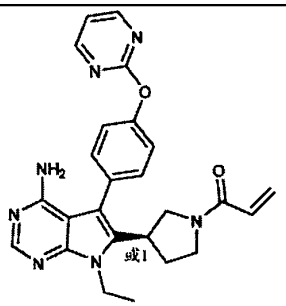
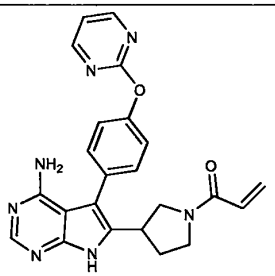
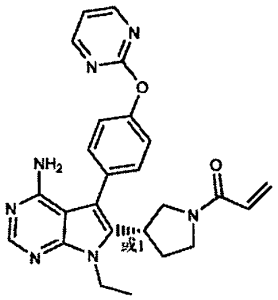
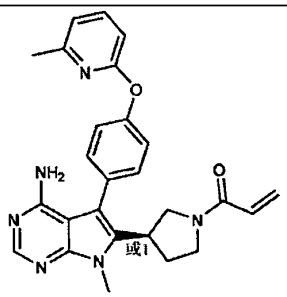
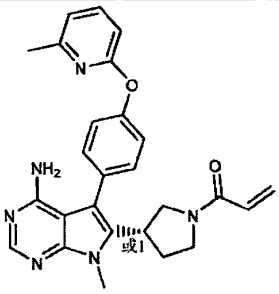
[0558]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
699		B	A
700		D	C
701		A	A
702		C	B
703		A	A

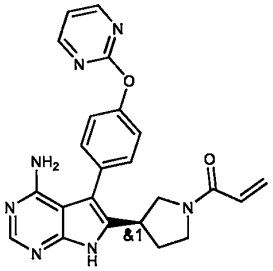
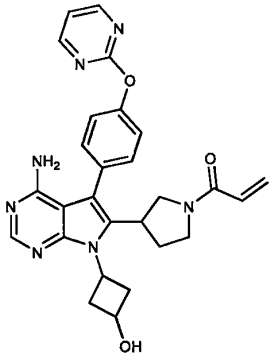
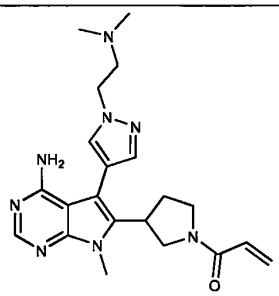
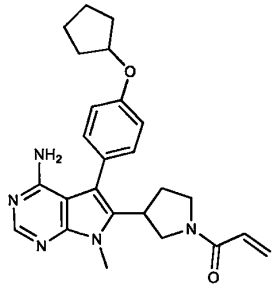
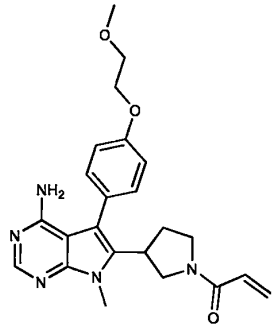
[0559]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
704		C	B
705		B	A
706		A	A
707		D	D

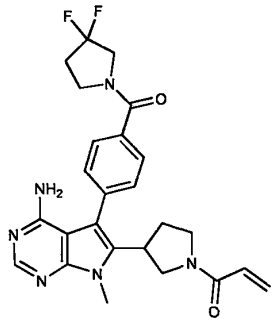
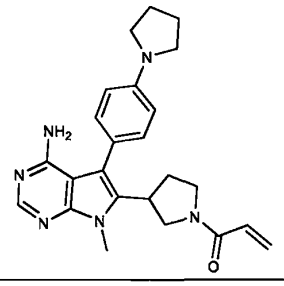
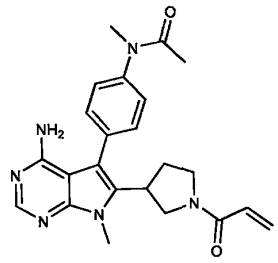
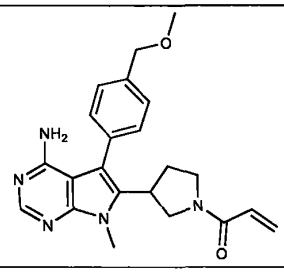
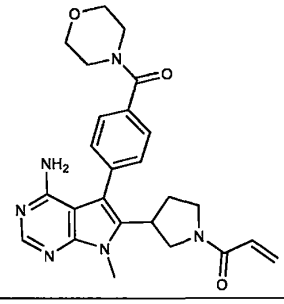
[0560]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
708		A	A
709		A	A
710		C	B
711		A	A
712		A	A

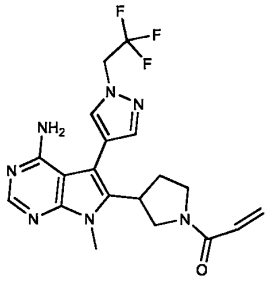
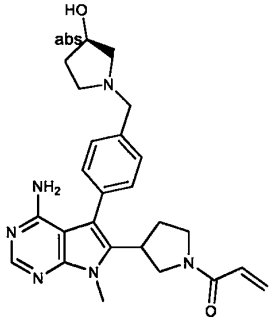
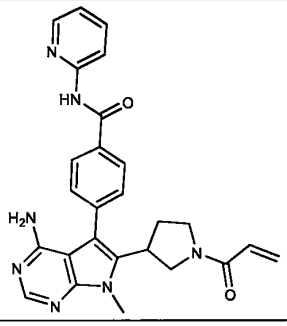
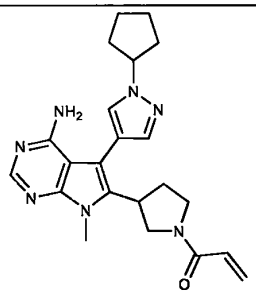
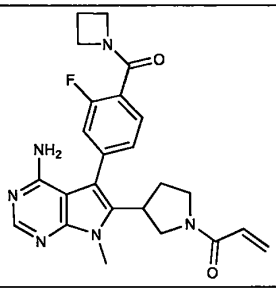
[0561]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
713		A	A
714		A	A
715		D	D
716		A	A
717		D	C

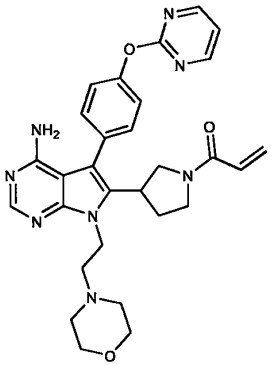
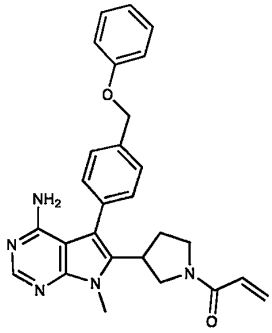
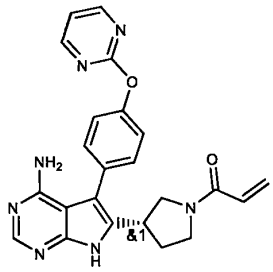
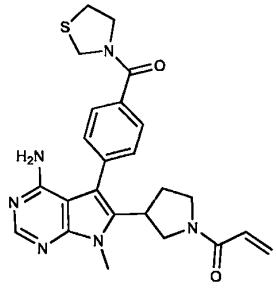
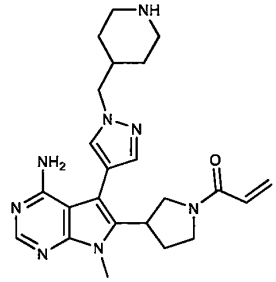
[0562]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
718		C	C
719		A	A
720		D	D
721		C	C
722		D	D

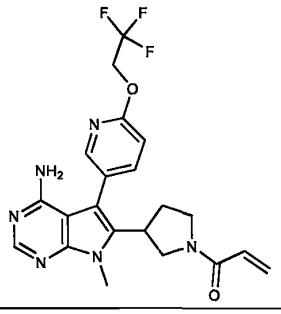
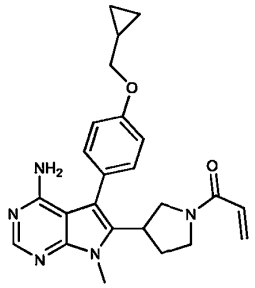
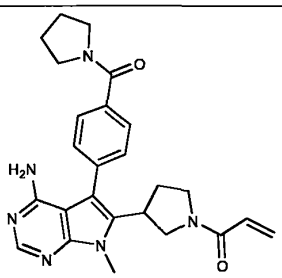
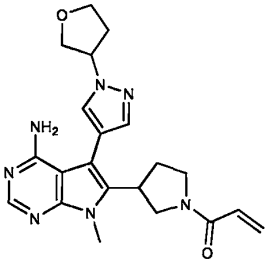
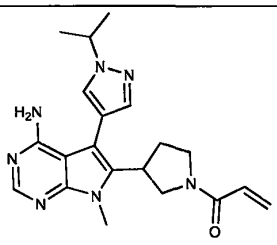
[0563]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
723		D	D
724		D	D
725		A	B
726		D	D
727		D	D

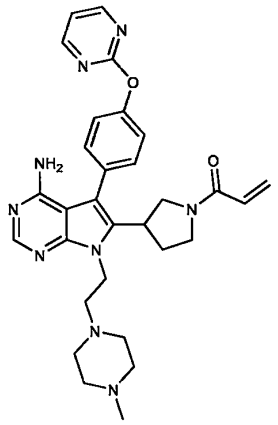
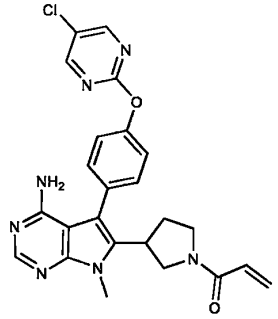
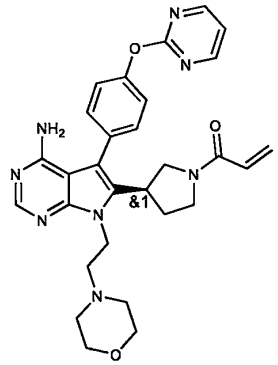
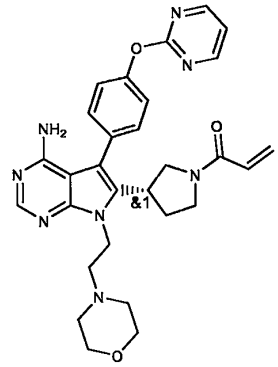
[0564]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
728		D	D
729		B	B
730		C	D
731		C	C
732		B	D

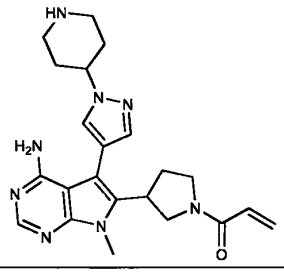
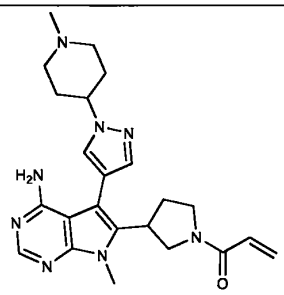
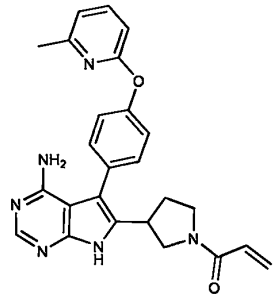
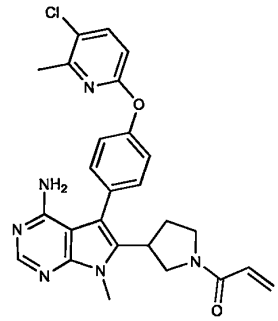
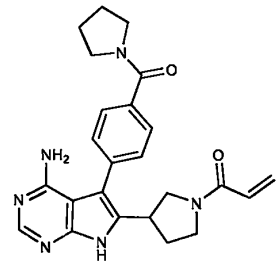
[0565]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
733		C	C
734		B	A
735		C	C
736		D	D
737		D	D

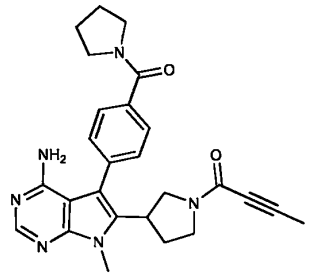
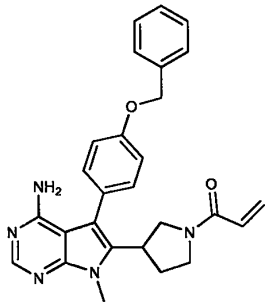
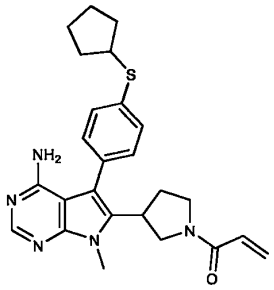
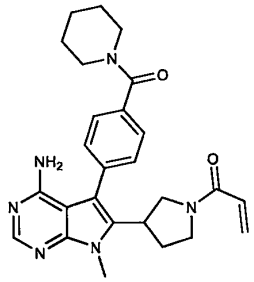
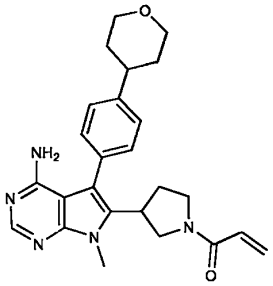
[0566]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
738		D	D
739		B	A
740		D	D
741		D	D

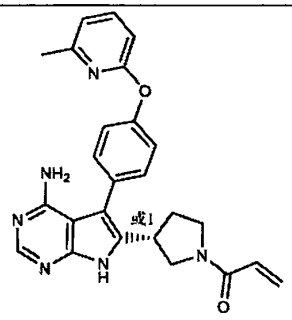
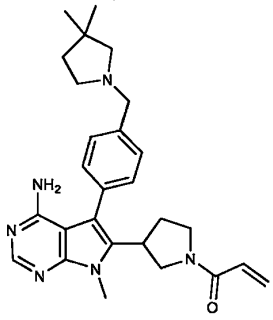
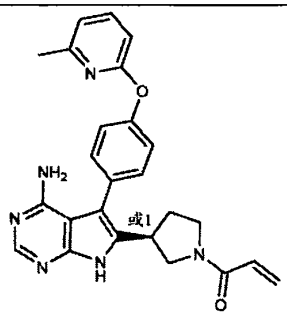
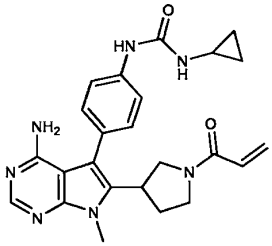
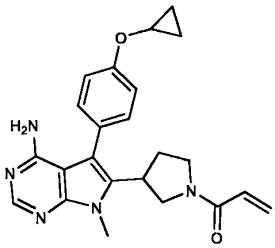
[0567]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
742		D	D
743		C	D
744		A	A
745		D	D
746		A	C

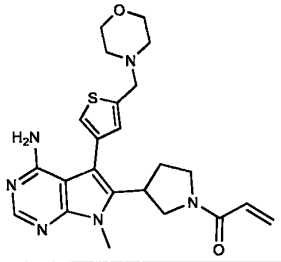
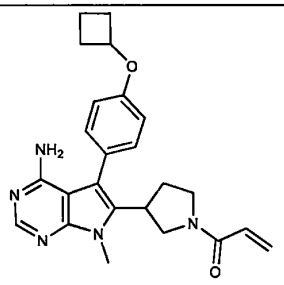
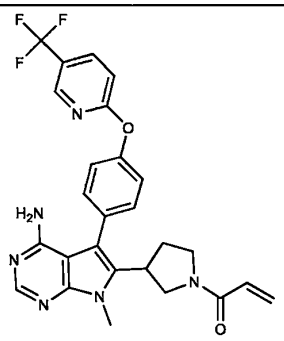
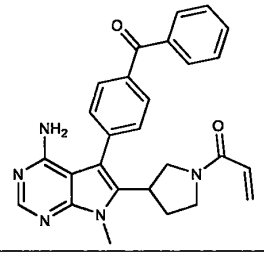
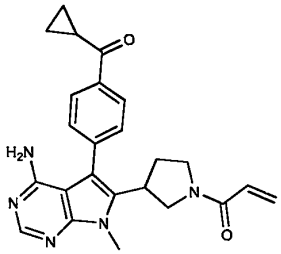
[0568]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
747		A	A
748		B	C
749		A	A
750		A	A
751		C	B

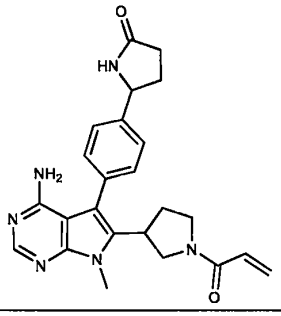
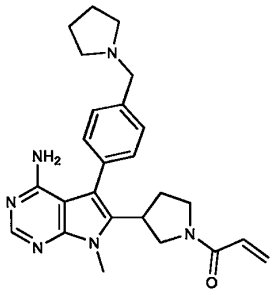
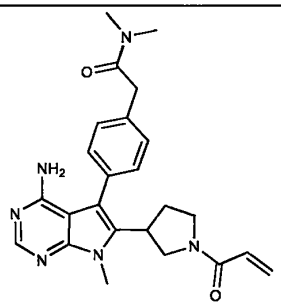
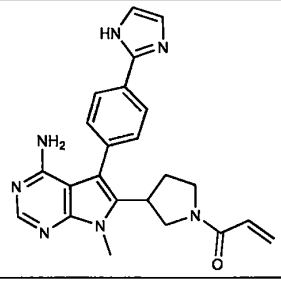
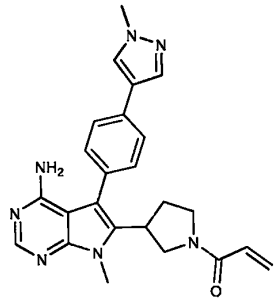
[0569]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
752		A	A
753		D	D
754		C	B
755		A	D
756		B	A

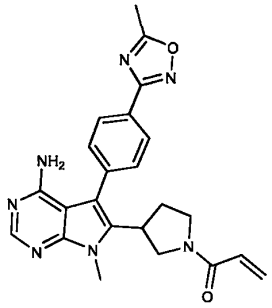
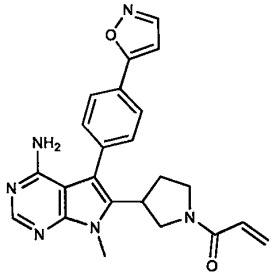
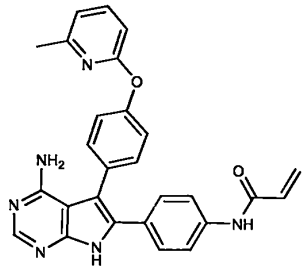
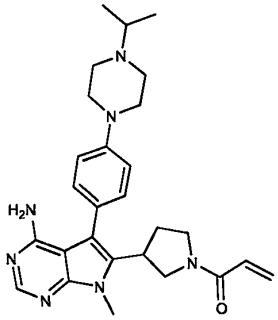
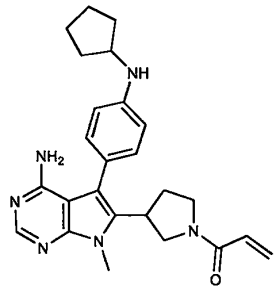
[0570]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
757		D	D
758		A	A
759		C	C
760		A	A
761		B	B

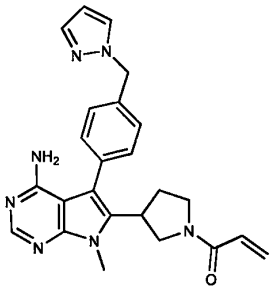
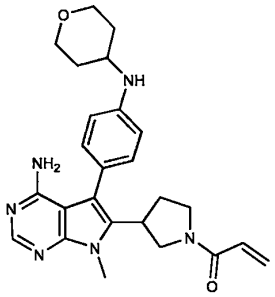
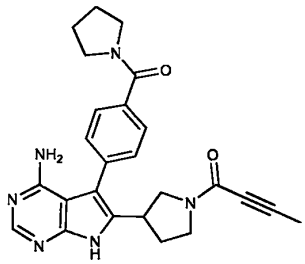
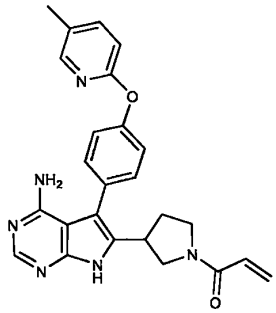
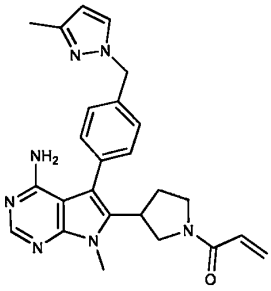
[0571]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
762		D	D
763		C	C
764		D	D
765		A	D
766		C	C

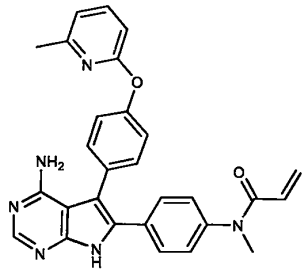
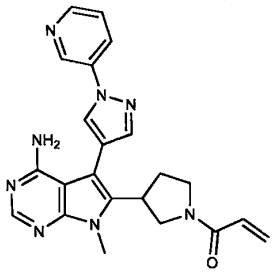
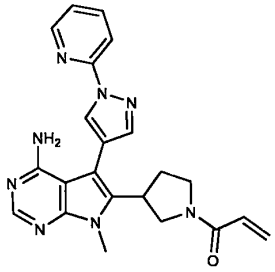
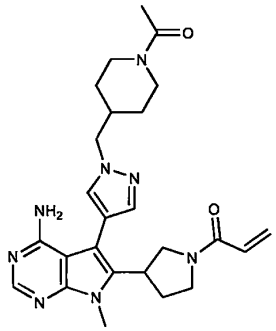
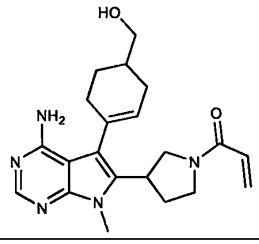
[0572]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
767		C	B
768		C	B
769		A	A
770			D
771		D	D

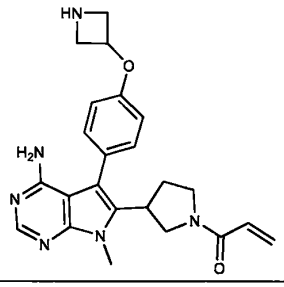
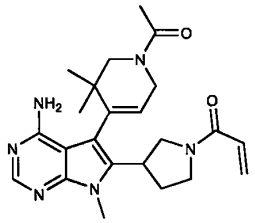
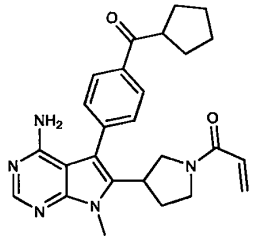
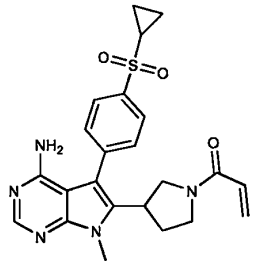
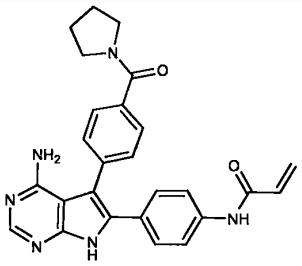
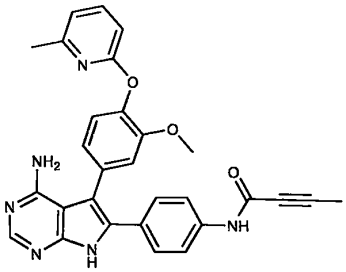
[0573]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
772		A	A
773		D	D
774		D	D
775		B	D
776		A	A

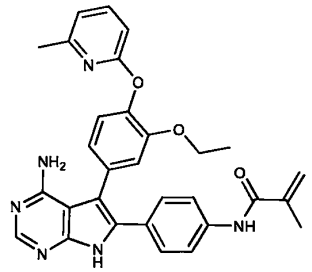
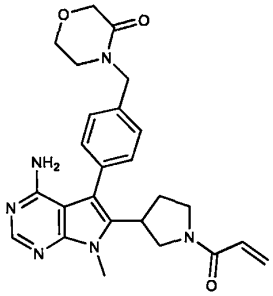
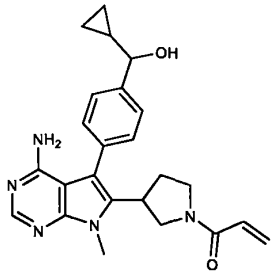
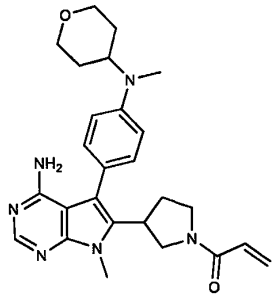
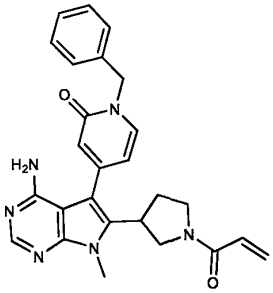
[0574]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
777		D	D
778		A	A
779		D	D
780		C	C
781		D	D

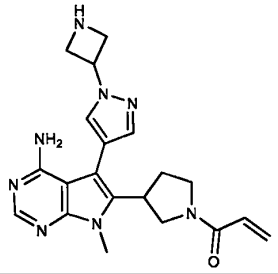
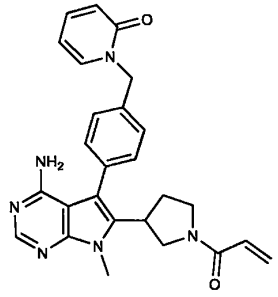
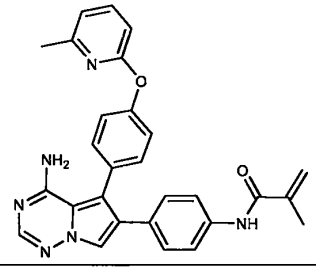
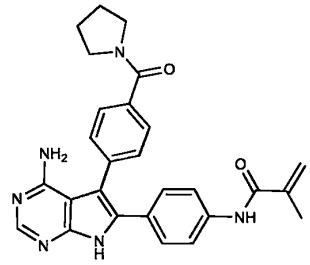
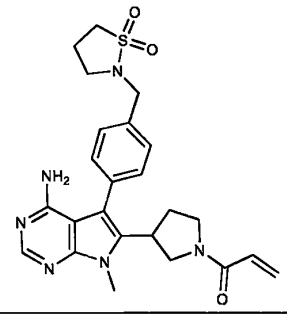
[0575]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
782		D	D
783		B	D
784		D	D
785		A	A
786		C	D
787		A	A

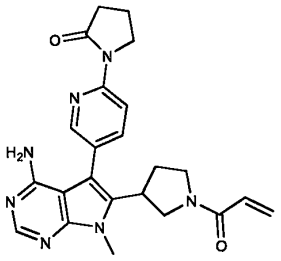
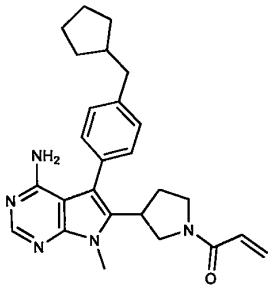
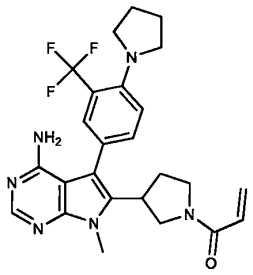
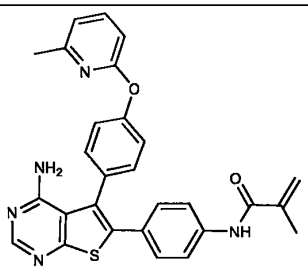
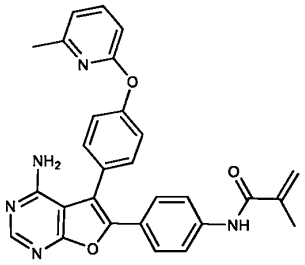
[0576]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
788		A	A
789		D	D
790		C	D
791		C	C
792		B	B

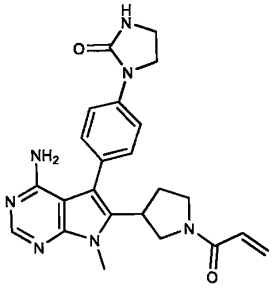
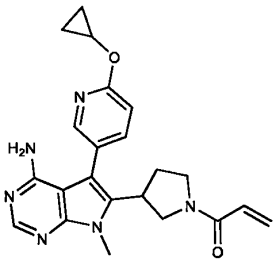
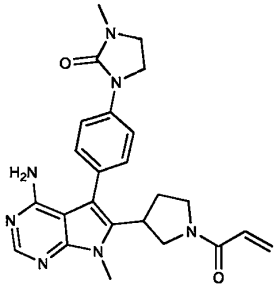
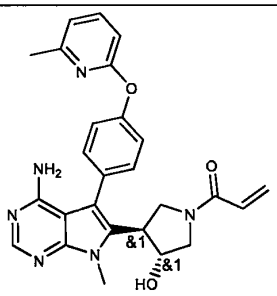
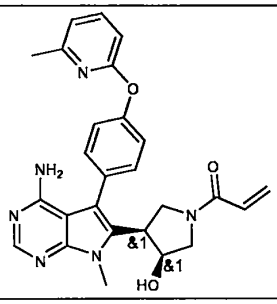
[0577]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
793		C	D
794		D	D
795		D	D
796		A	A
797		C	C

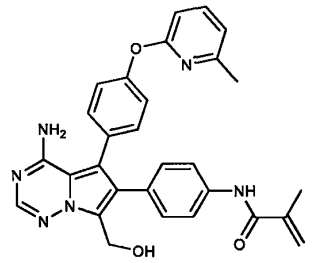
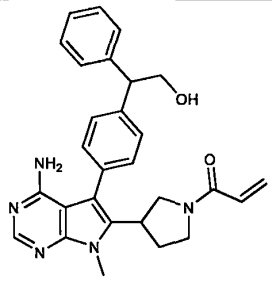
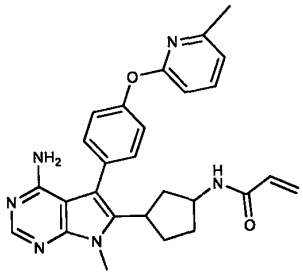
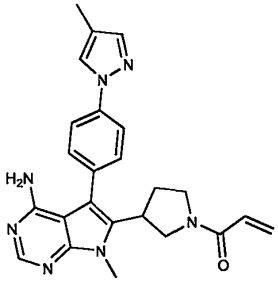
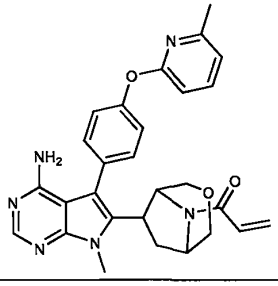
[0578]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
798		C	D
799		C	C
800		A	A
801		A	A
802		D	D

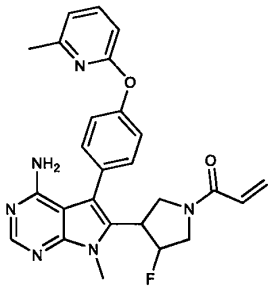
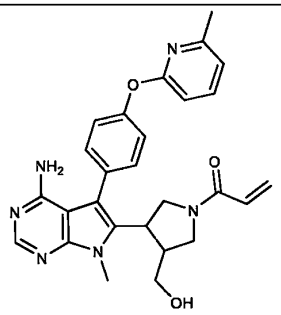
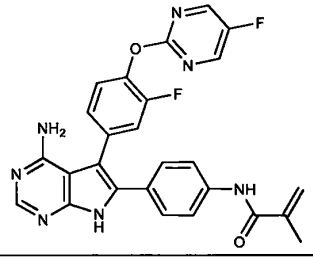
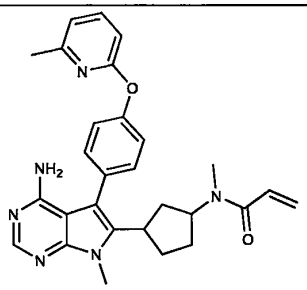
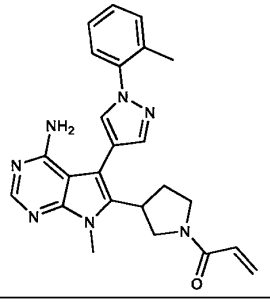
[0579]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
803		D	D
804		B	D
805		D	C
806		A	B
807		C	C

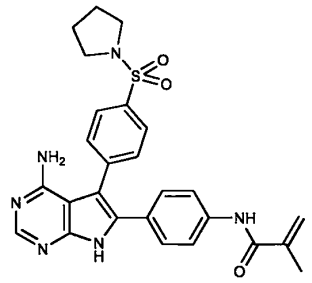
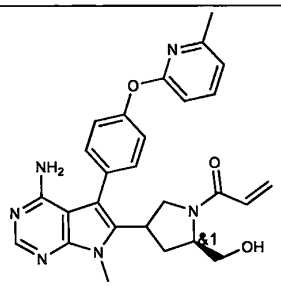
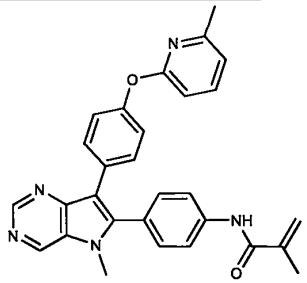
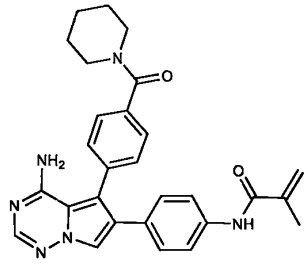
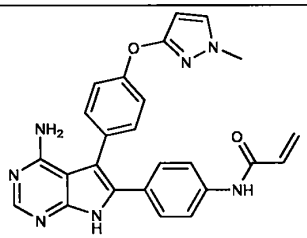
[0580]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
808		B	B
809		A	A
810		A	A
811		B	C
812		A	A

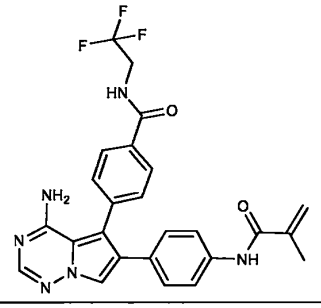
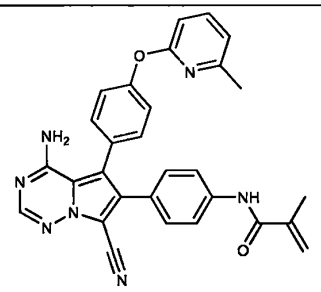
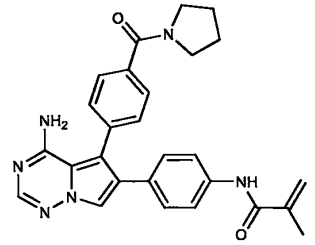
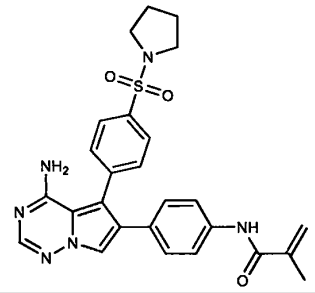
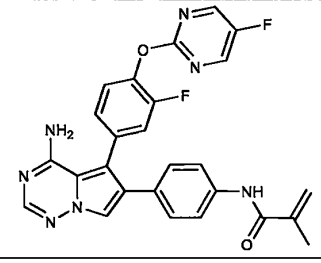
[0581]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
813		C	C
814		A	A
815		C	D
816		C	B
817		B	B

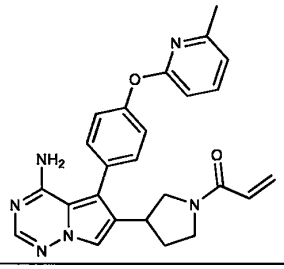
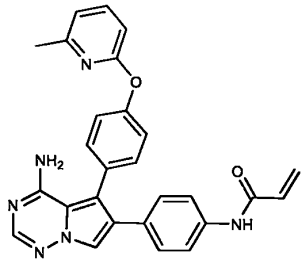
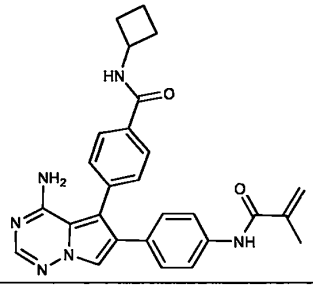
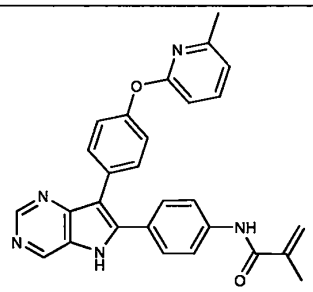
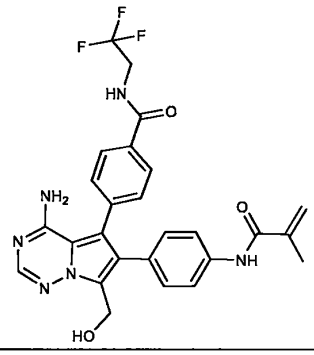
[0582]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
818		C	C
819		C	C
820		A	A
821		D	D
822		C	C

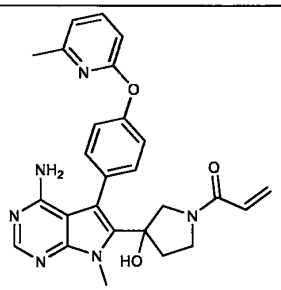
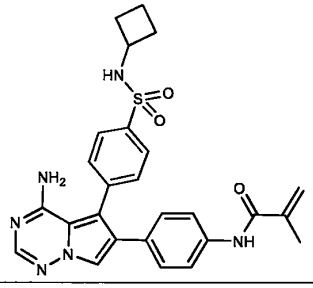
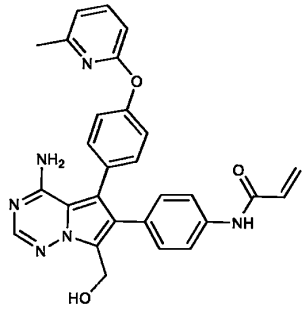
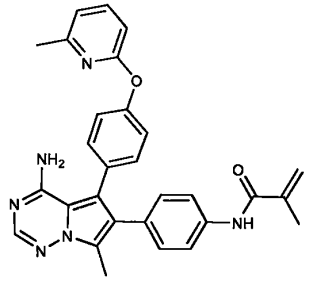
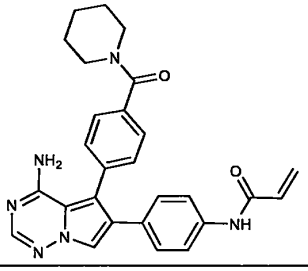
[0583]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
823		B	C
824		B	C
825		B	A
826		C	C
827		D	D

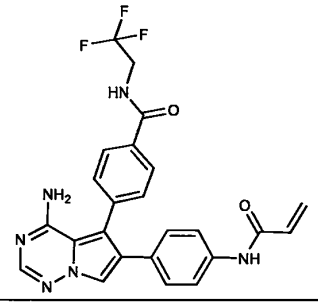
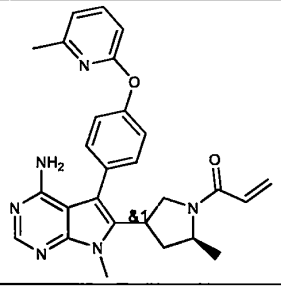
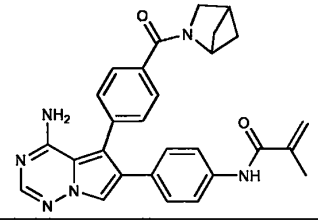
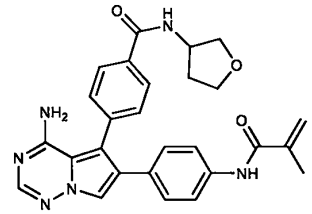
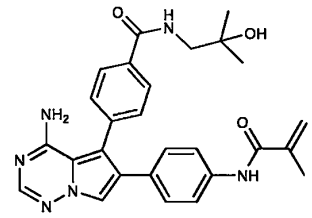
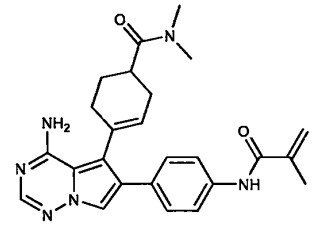
[0584]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
828		D	C
829		A	A
830		A	A
831		A	B
832		D	D

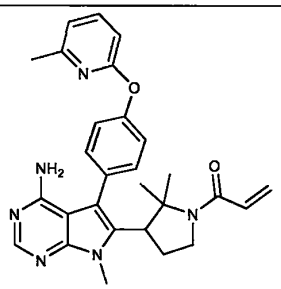
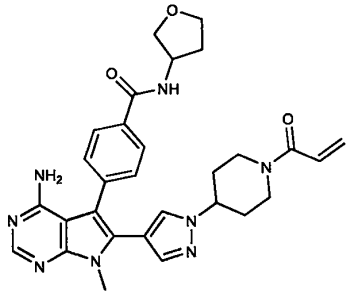
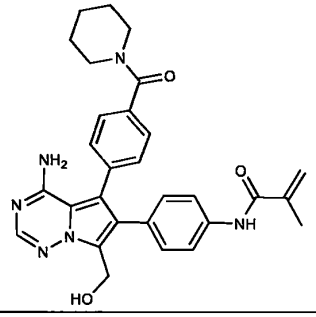
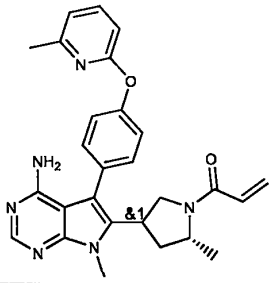
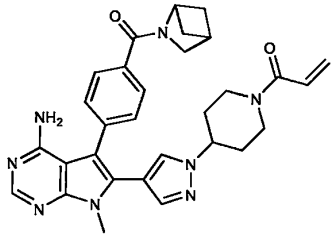
[0585]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
833		B	C
834		C	C
835		D	D
836		A	A
837		A	A

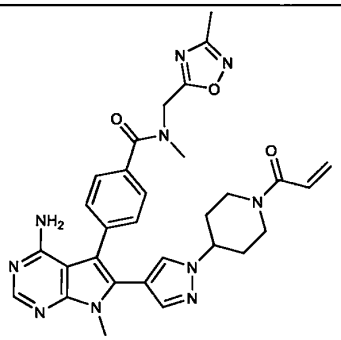
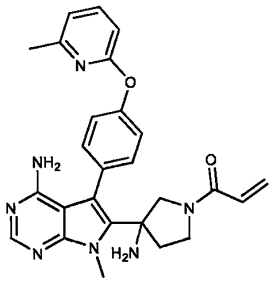
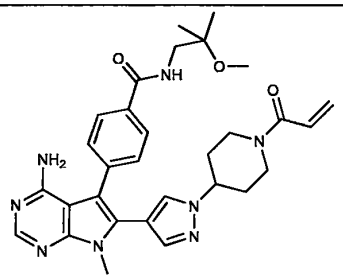
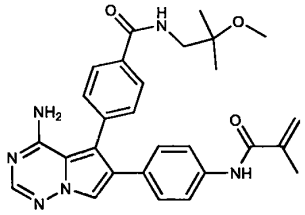
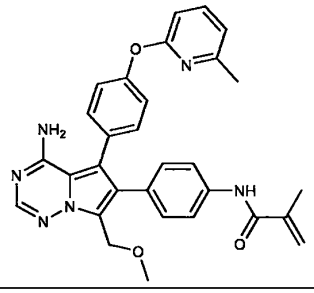
[0586]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
838		A	A
839		A	A
840		A	A
841		C	C
842		C	D
843		C	C

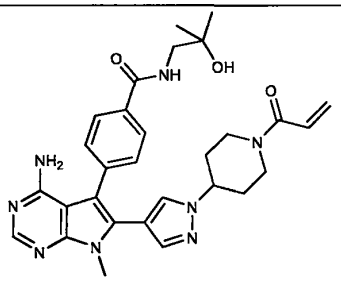
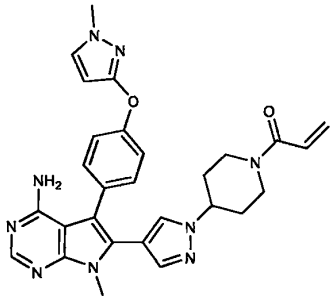
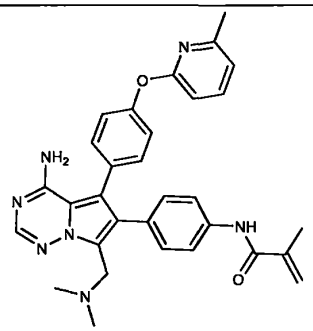
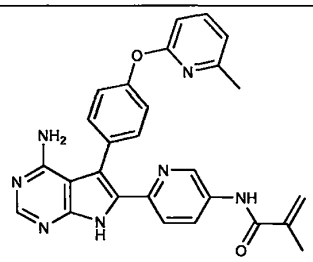
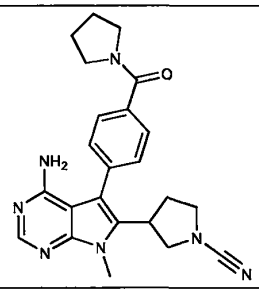
[0587]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
844		D	D
845		C	C
846		A	D
847		C	C
848		B	B

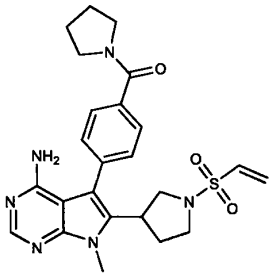
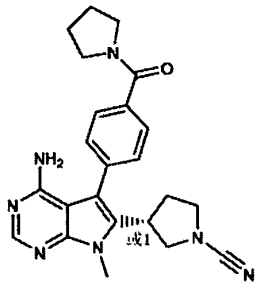
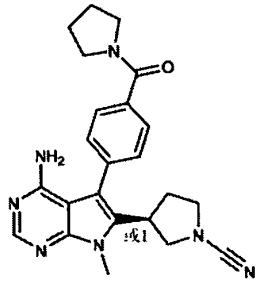
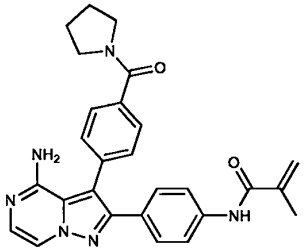
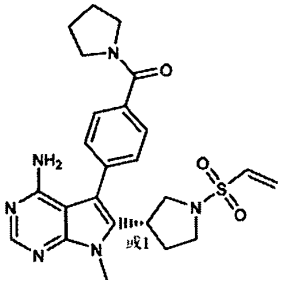
[0588]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
849		B	C
850		D	D
851		D	D
852		C	D
853		C	B

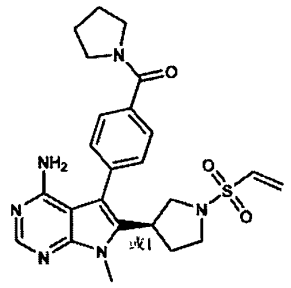
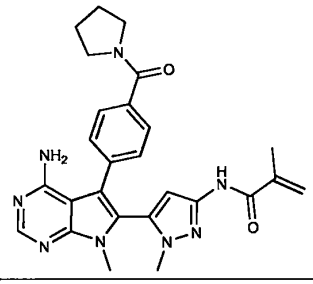
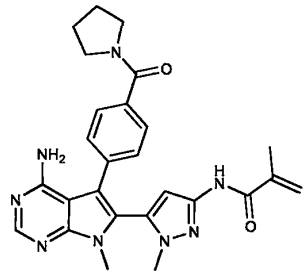
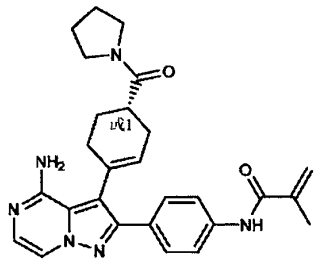
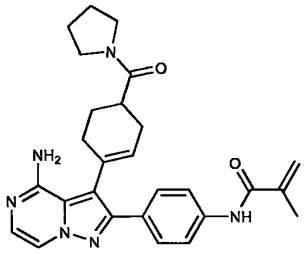
[0589]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
854		B	A
855		C	D
856		C	C
857		D	D
858		A	A

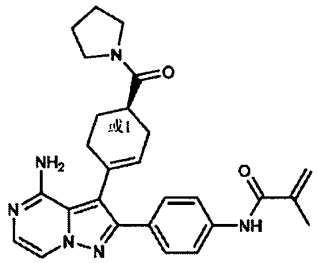
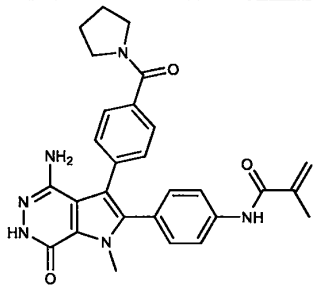
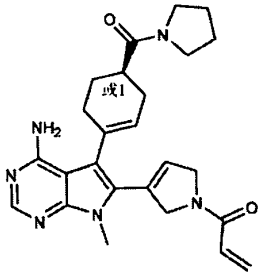
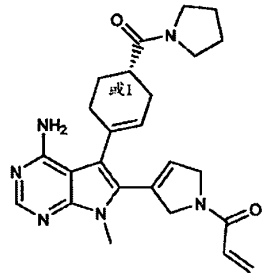
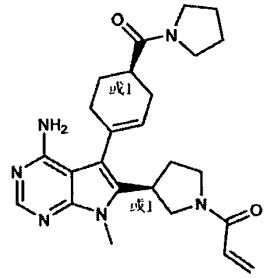
[0590]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
859		D	D
860		A	C
861		D	D
862		D	D
863		C	B

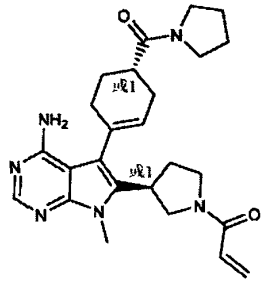
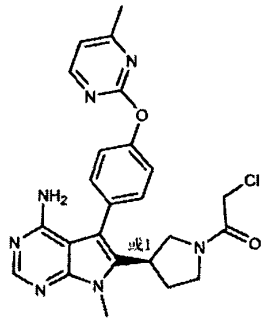
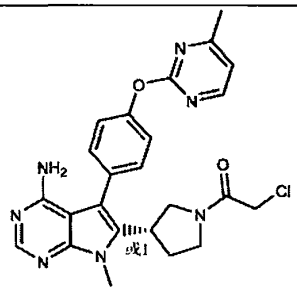
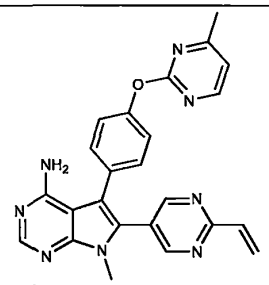
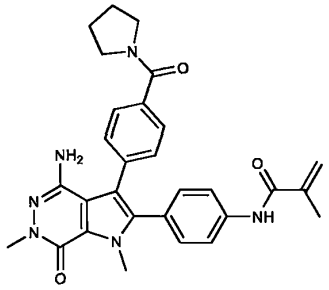
[0591]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
864		A	B
865		B	C
866		A	A
867		A	A
868		D	D

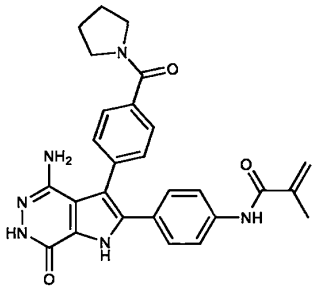
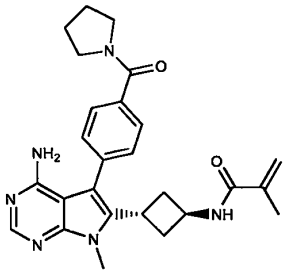
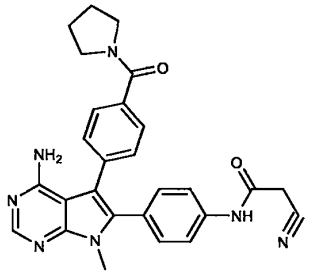
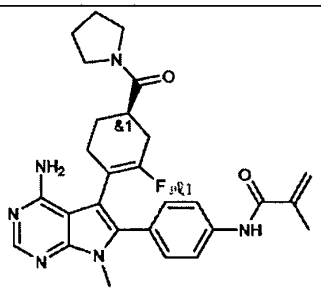
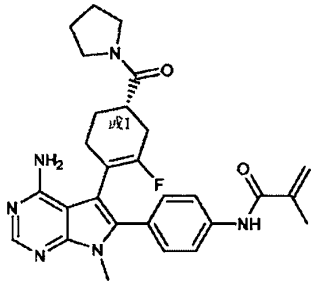
[0592]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
869		D	C
870		D	B
871		C	C
872		B	B
873		D	C

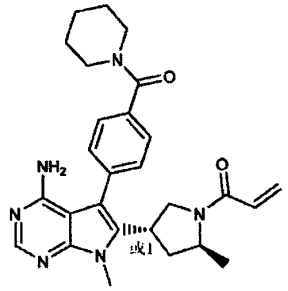
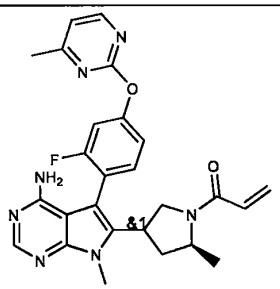
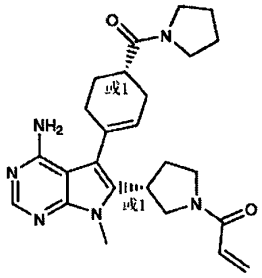
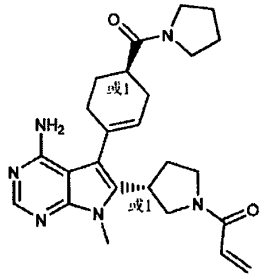
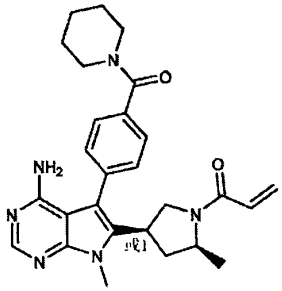
[0593]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
874		C	B
875		C	C
876		A	A
877		B	C
878		B	A

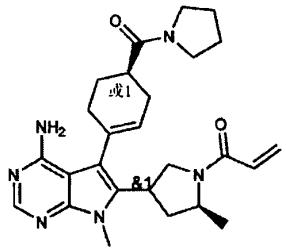
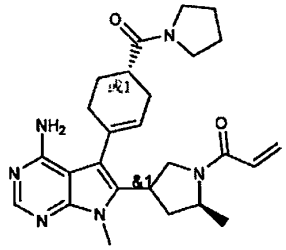
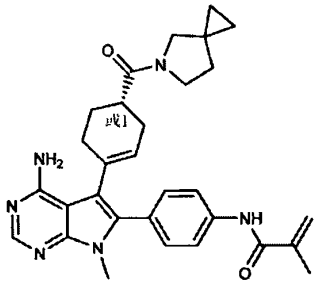
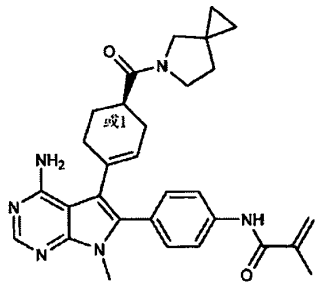
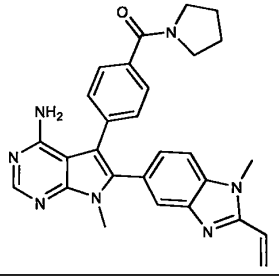
[0594]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
879		D	D
880		D	D
881		D	D
882		D	D
883		D	D

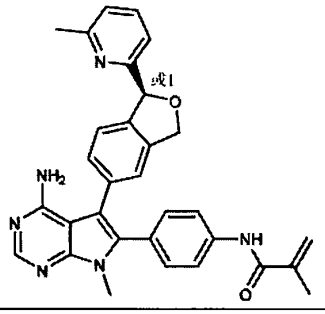
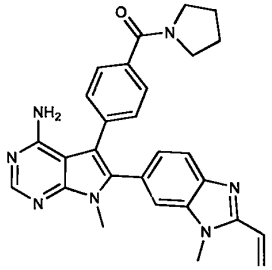
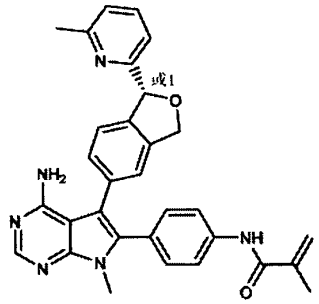
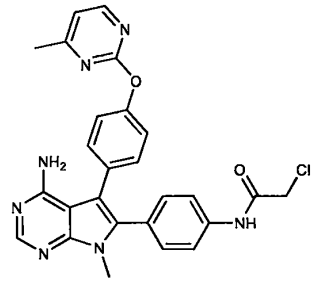
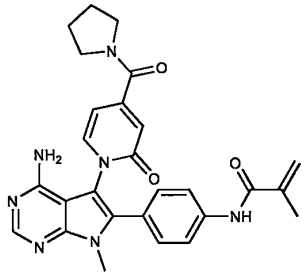
[0595]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
884		D	B
885		D	D
886		C	A
887		D	D
888		D	D

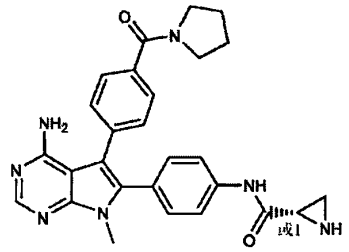
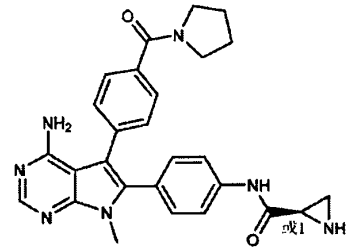
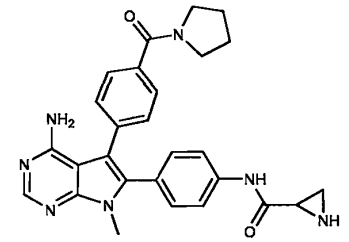
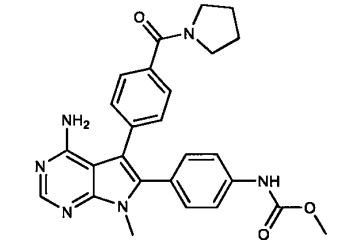
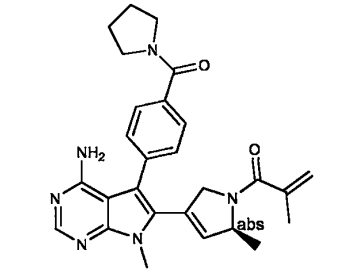
[0596]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
889		C	B
890		D	D
891		D	D
892		B	A
893		D	D

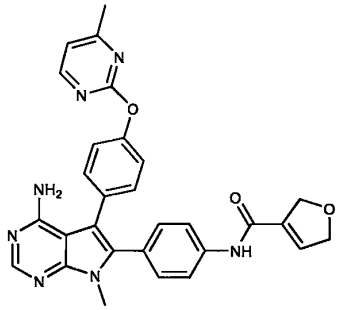
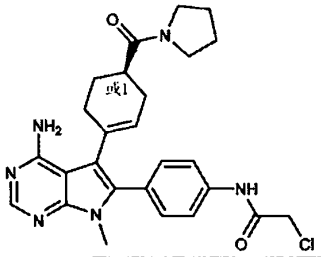
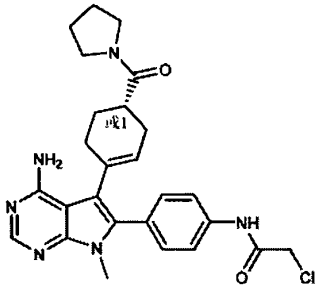
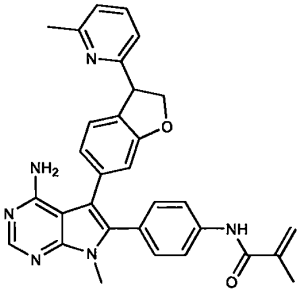
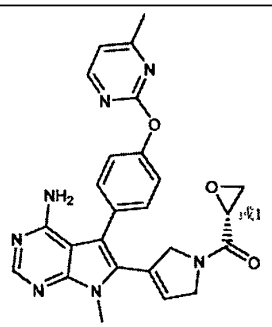
[0597]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
894		C	C
895		D	D
896		B	C
897		B	A
898		A	A

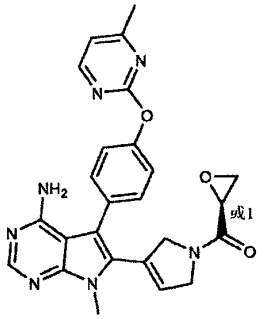
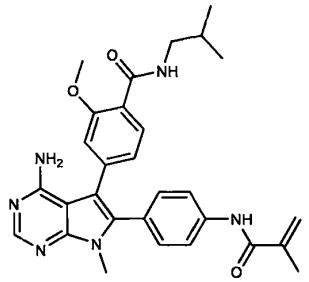
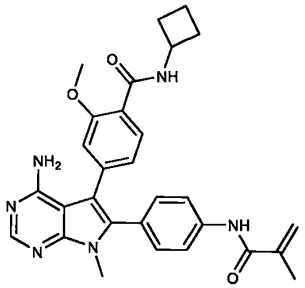
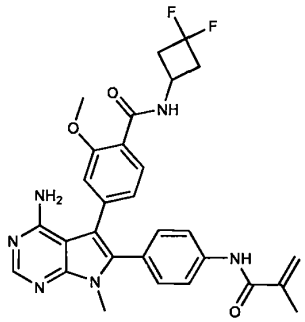
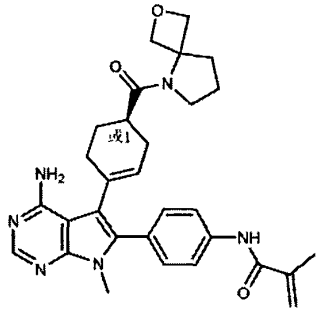
[0598]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
899		D	D
900		D	D
901		D	D
902		D	D
903		D	D

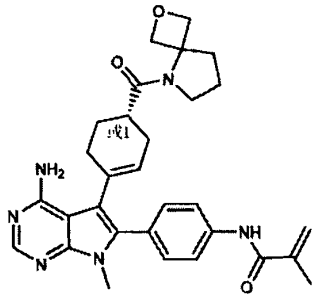
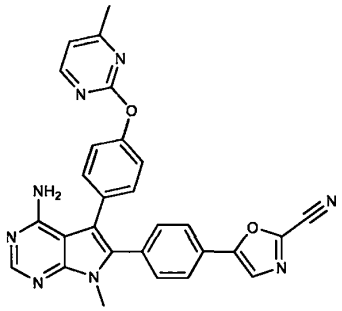
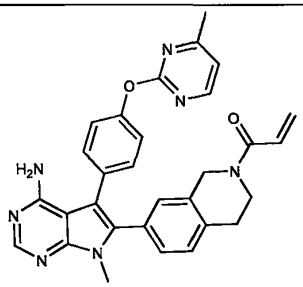
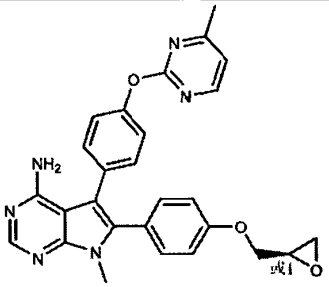
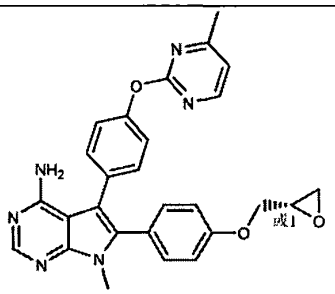
[0599]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
904		D	D
905		B	A
906		A	A
907		A	A
908		B	A

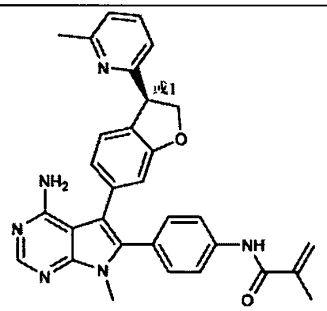
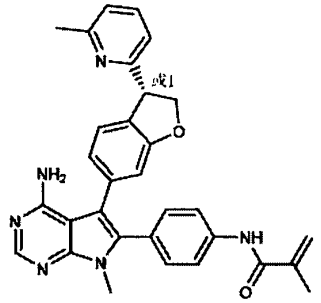
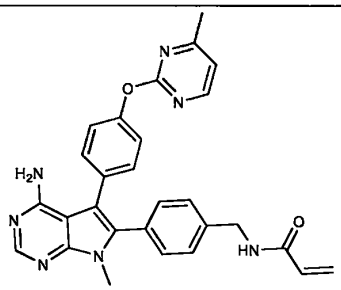
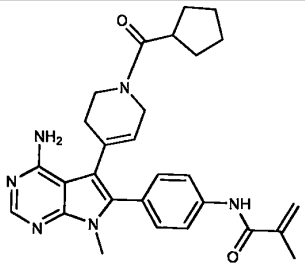
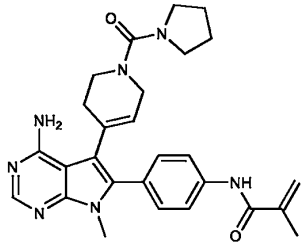
[0600]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
909		D	D
910		D	D
911		A	A
912		A	A
913		A	A

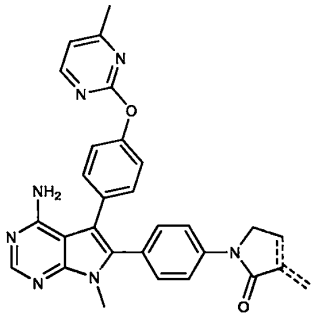
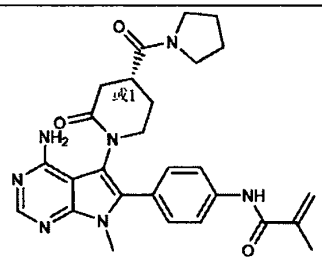
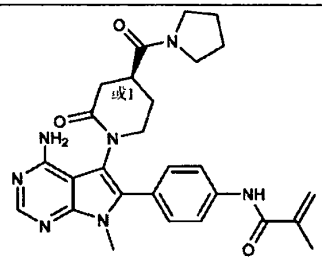
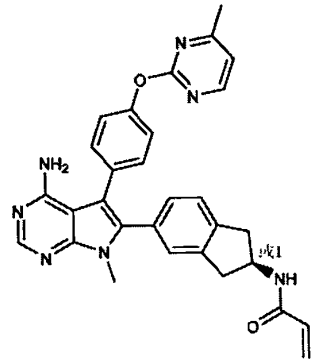
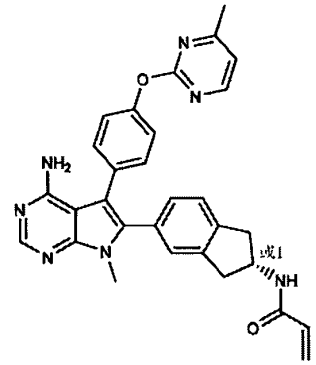
[0601]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
914		A	A
915		D	C
916		D	B
917		B	B
918		C	D

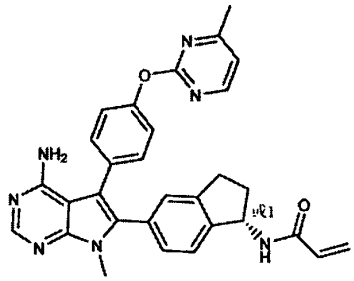
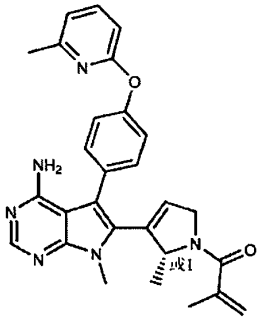
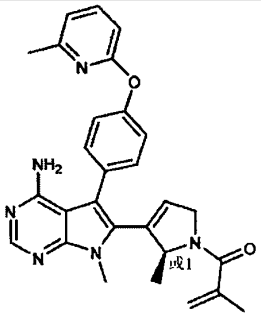
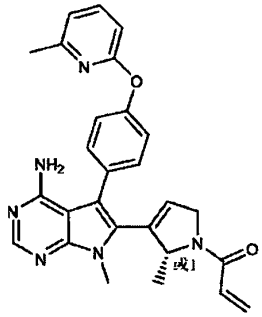
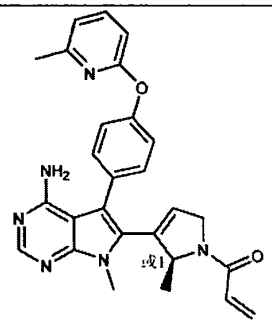
[0602]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
919		B	D
920		A	A
921		D	C
922		C	C
923		D	C

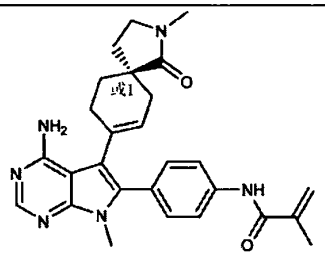
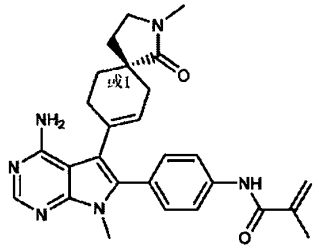
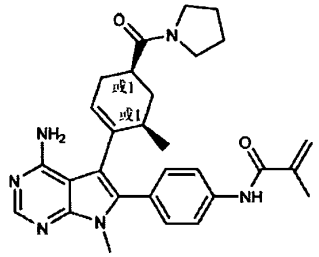
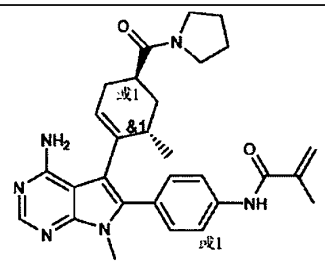
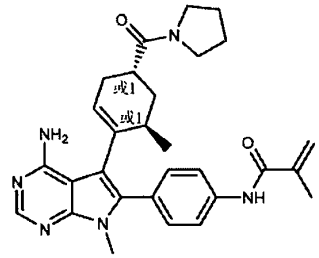
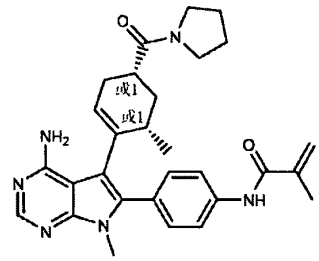
[0603]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
924		D	D
925		A	A
926		D	D
927		D	D
928		C	C

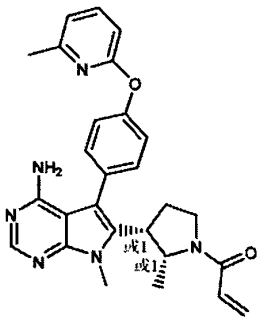
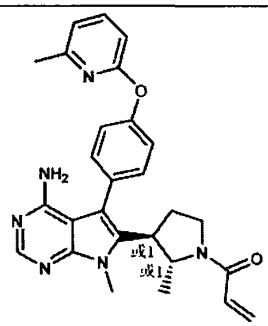
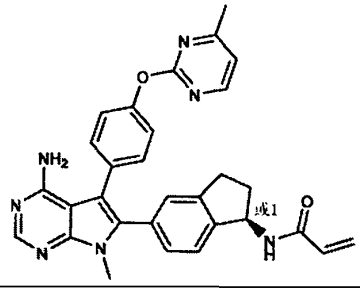
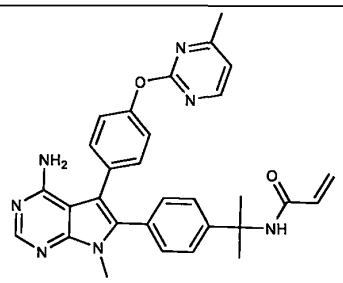
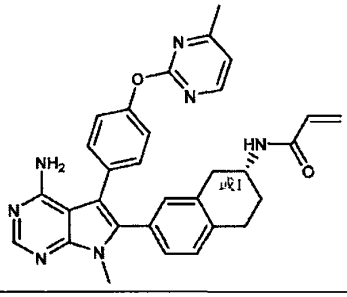
[0604]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
929		C	B
930		C	B
931		C	D
932		B	C
933		A	A

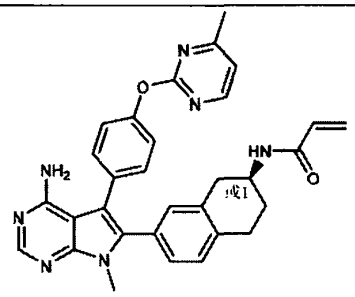
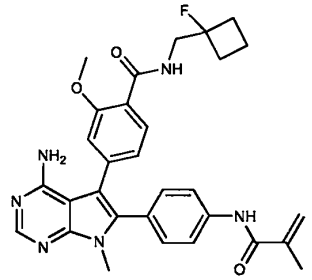
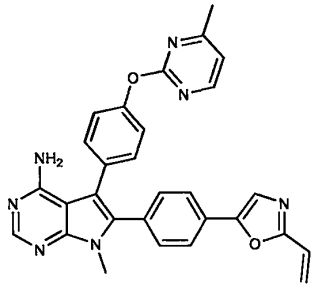
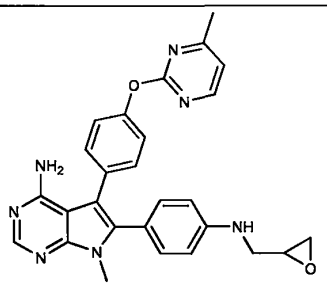
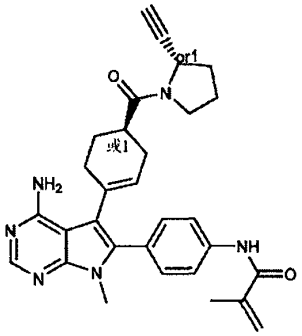
[0605]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
934		A	A
935		D	D
936		D	C
937		D	D
938		D	D
939		D	D

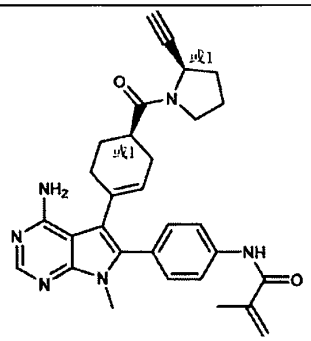
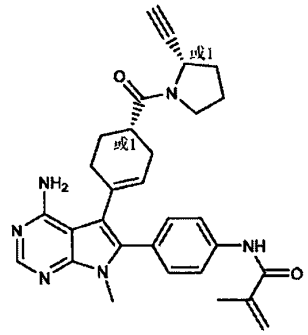
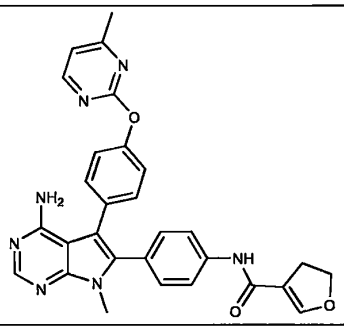
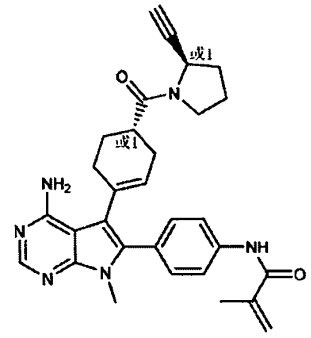
[0606]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
940		D	D
941		C	B
942		C	C
943		C	C
944		D	D

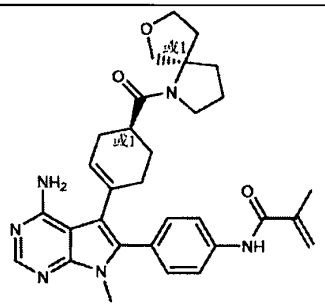
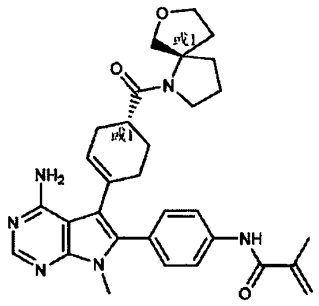
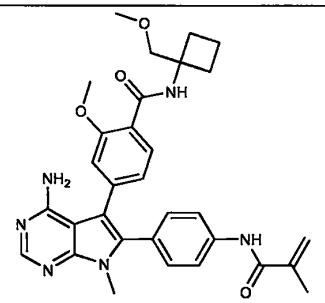
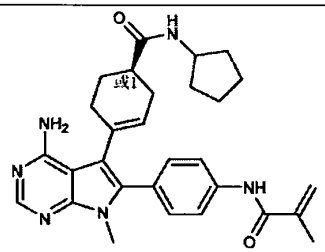
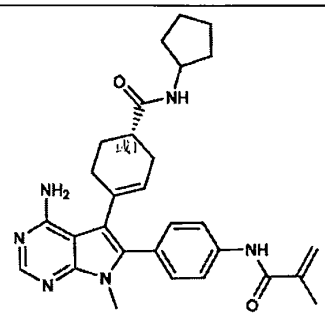
[0607]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
945		D	D
946		C	D
947		A	A
948		D	D
949		B	D

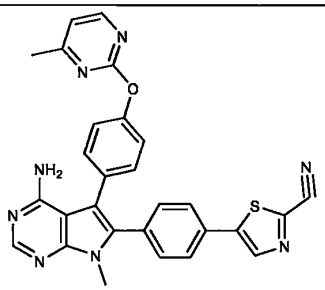
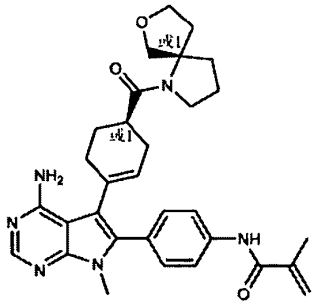
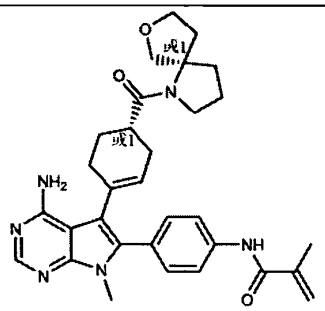
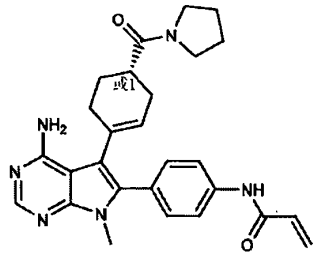
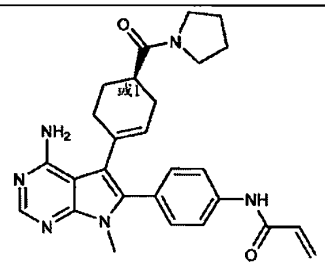
[0608]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
950		D	D
951		C	B
952		A	A
953		A	D

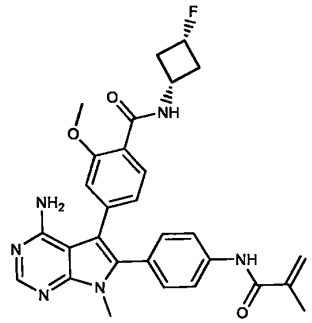
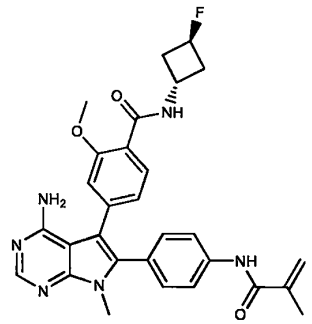
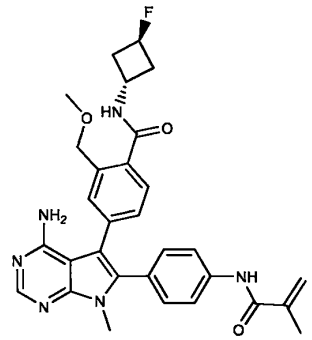
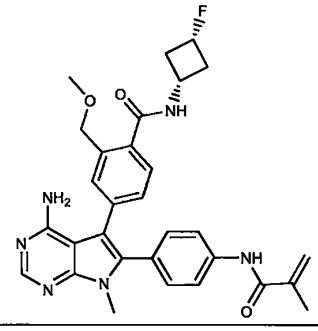
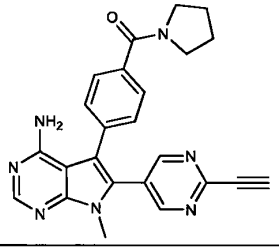
[0609]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
954		A	A
955		D	C
956		A	A
957		B	A
958		C	A

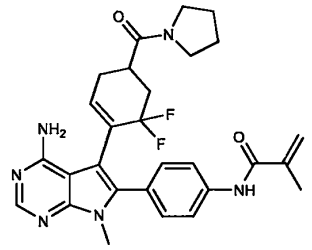
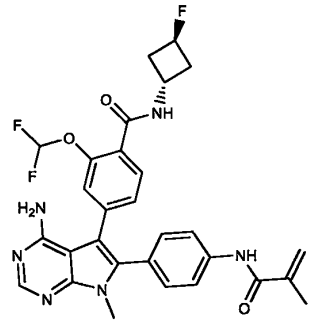
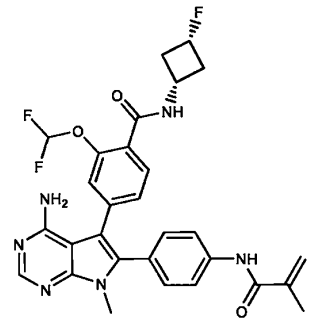
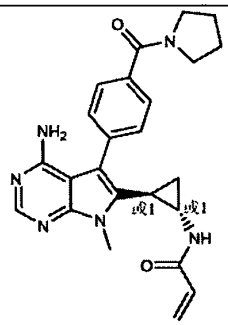
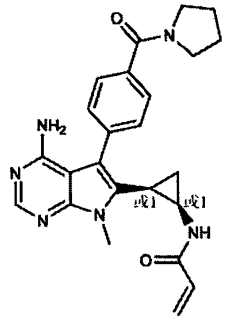
[0610]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
959		C	A
960		D	D
961		D	C
962		A	A
963		A	A

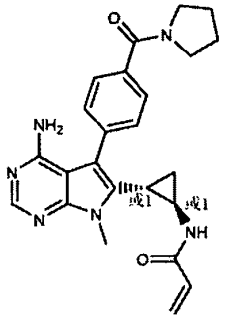
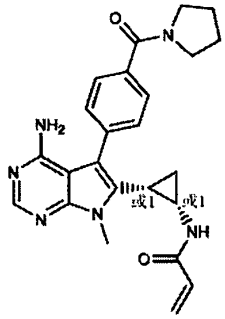
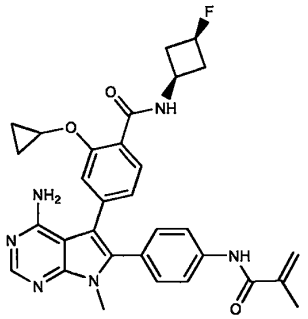
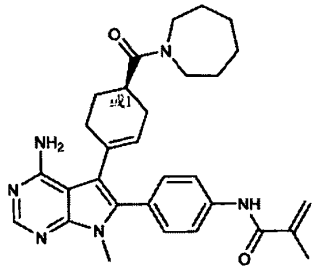
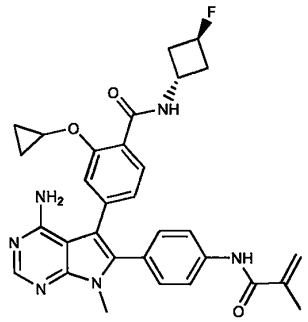
[0611]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
964		A	A
965		A	A
966		A	A
967		D	D
968		C	C

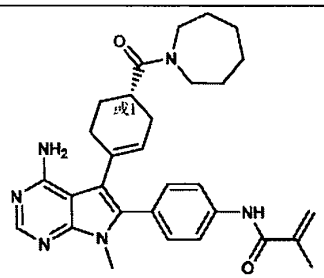
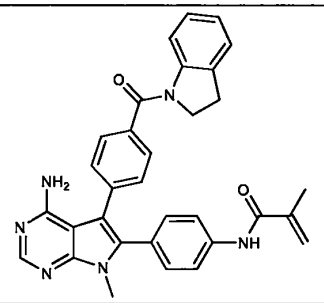
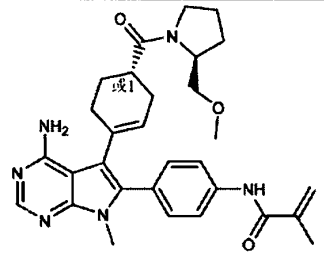
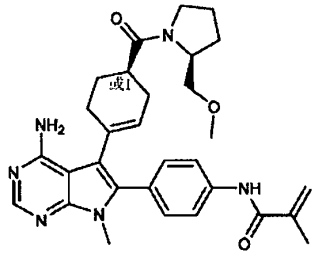
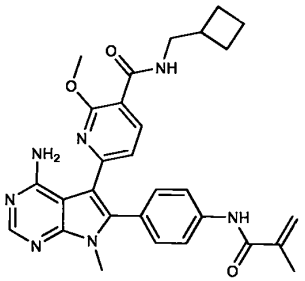
[0612]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
969		A	A
970		D	D
971		C	C
972		D	D
973		C	D

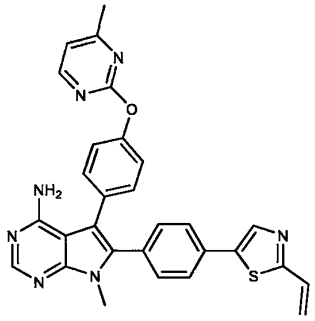
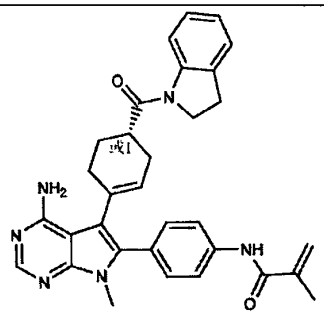
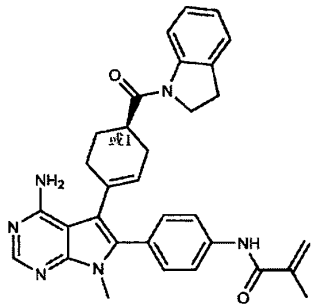
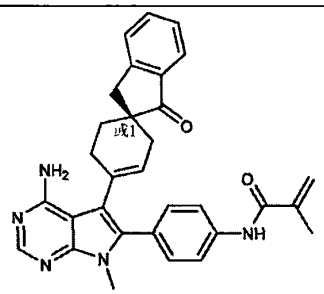
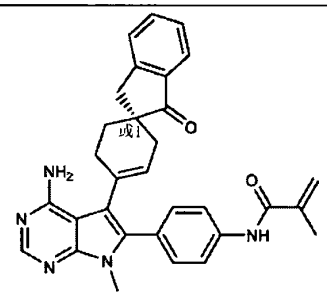
[0613]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
974		D	D
975		D	D
976		D	D
977		A	A
978		C	C

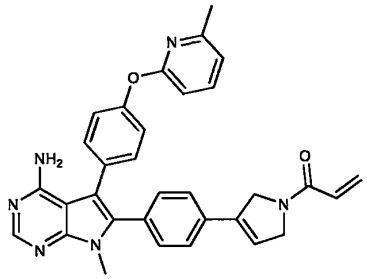
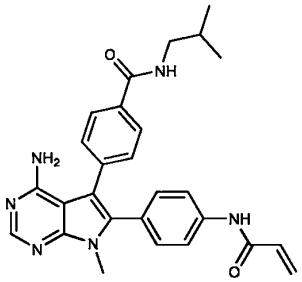
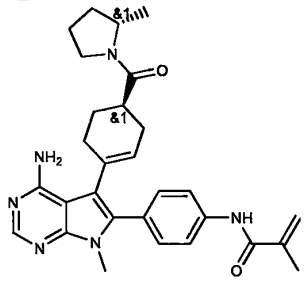
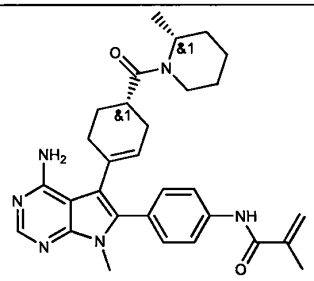
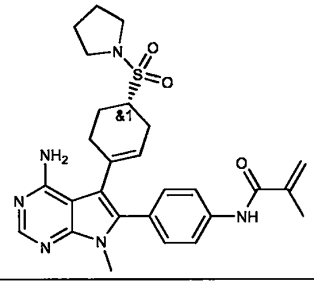
[0614]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
979		C	C
980		A	A
981		C	C
982		D	C
983		A	A

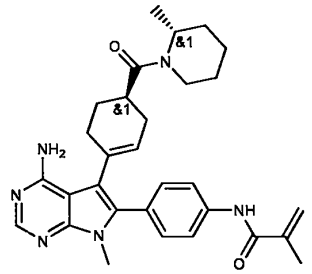
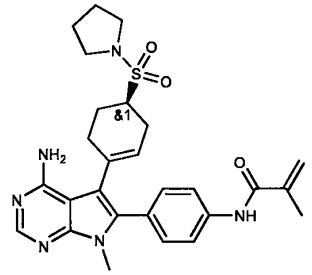
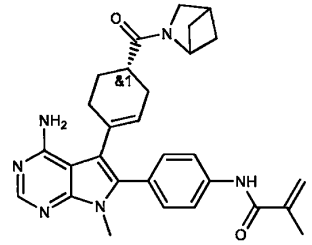
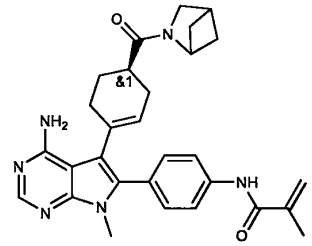
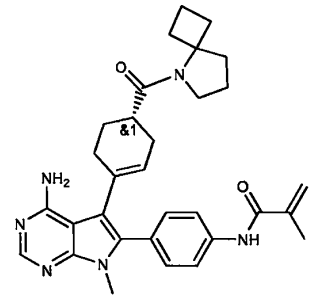
[0615]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
984		A	A
985		C	C
986		C	C
987		D	D
988		C	A

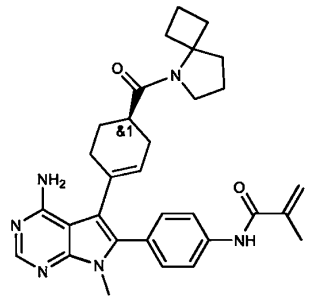
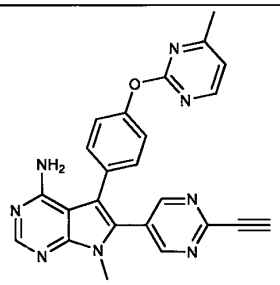
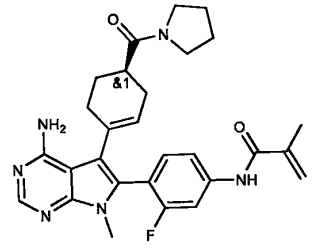
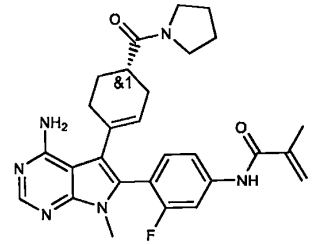
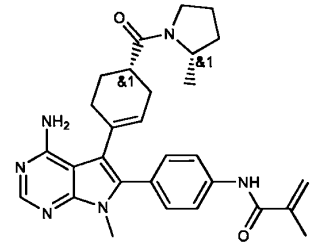
[0616]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
989		D	C
990		A	A
991		A	A
992		D	B
993		A	A

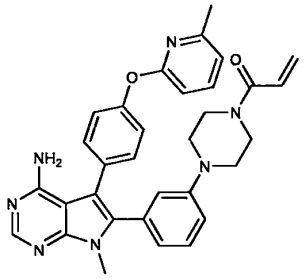
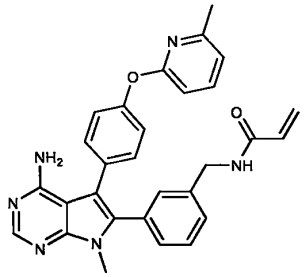
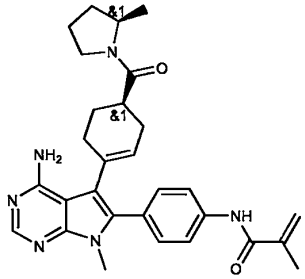
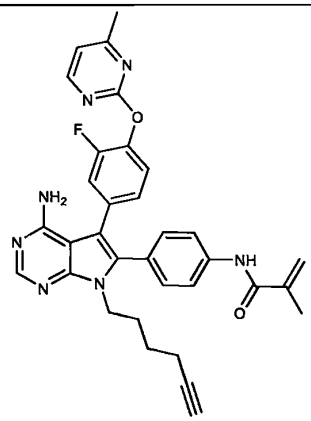
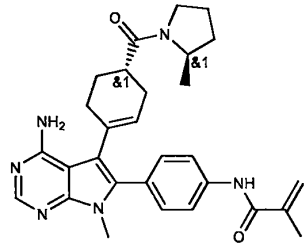
[0617]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
994		D	B
995		D	C
996		C	B
997		D	C
998		A	A

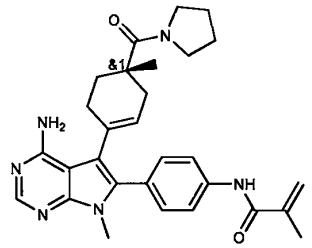
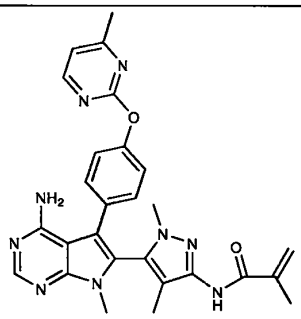
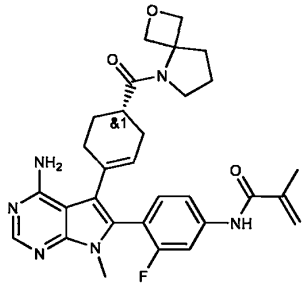
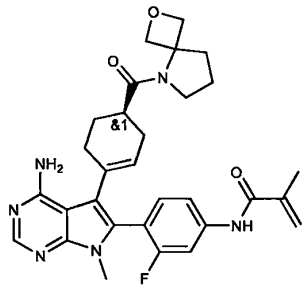
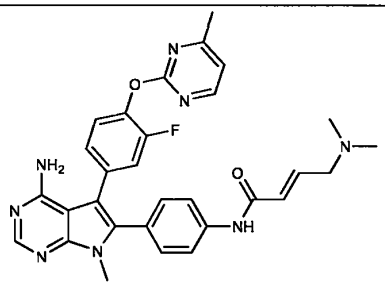
[0618]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
999		A	A
1000		D	C
1001		A	A
1002		A	A
1003		C	B

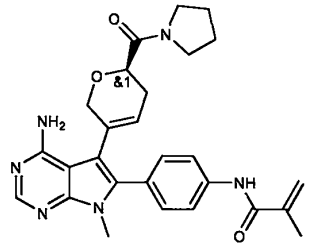
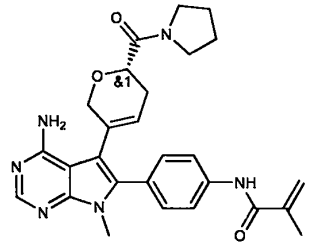
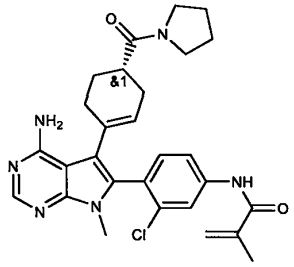
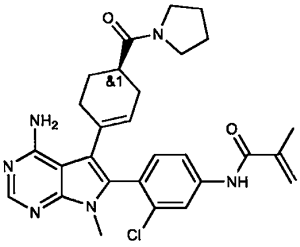
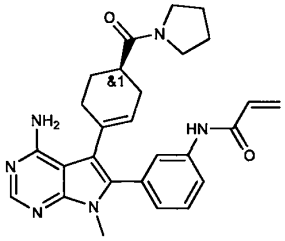
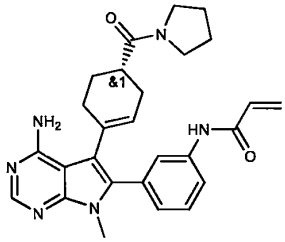
[0619]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1004		A	A
1005		C	B
1006		C	C
1007		A	A
1008		B	B

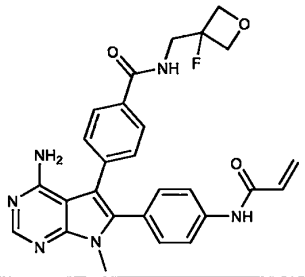
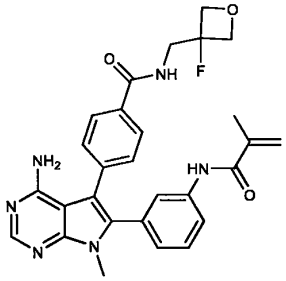
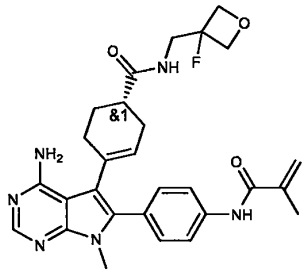
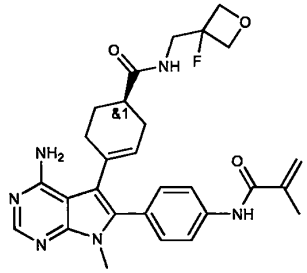
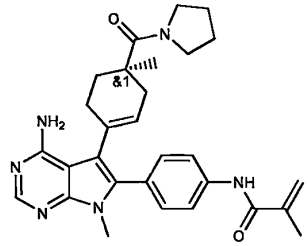
[0620]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1009		D	C
1010		D	C
1011		A	A
1012		C	B
1013		A	A

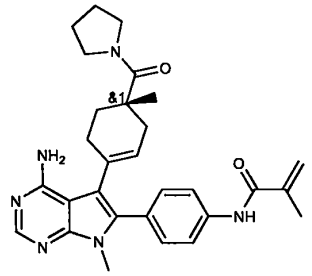
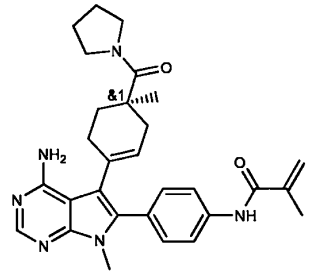
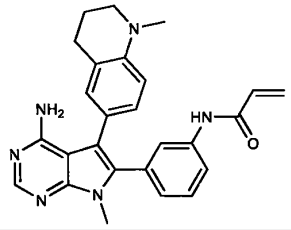
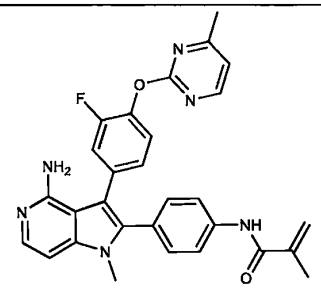
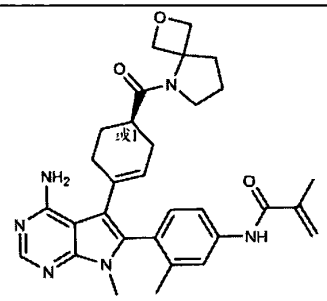
[0621]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1014		A	A
1015		D	D
1016		D	D
1017		A	A
1018		A	A
1019		A	A

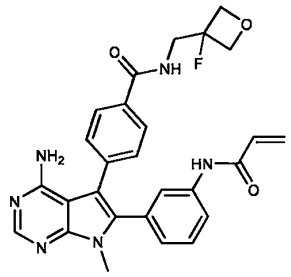
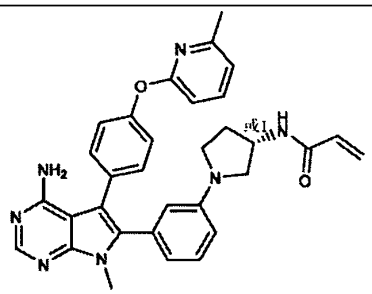
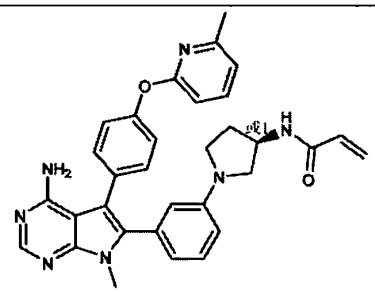
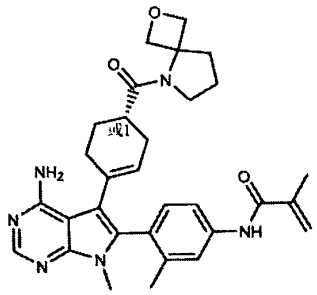
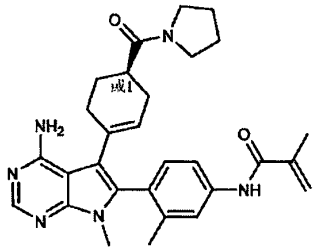
[0622]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1020		B	A
1021		A	A
1022		C	D
1023		D	D
1024		C	C

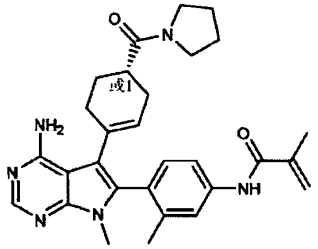
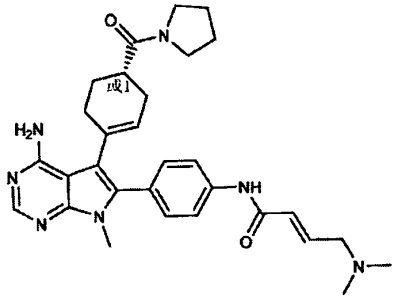
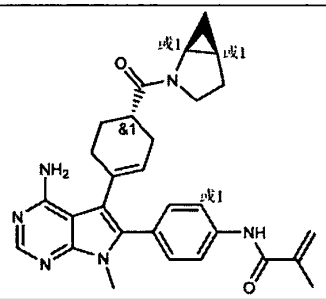
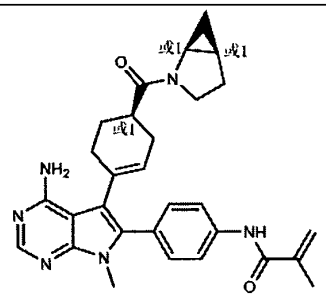
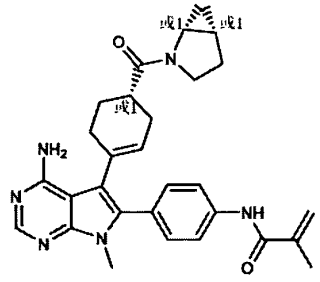
[0623]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1025		D	D
1026		D	D
1027		D	D
1028		A	A
1029		D	C

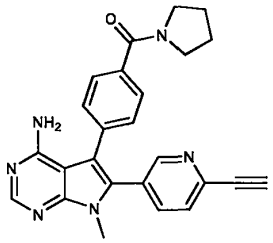
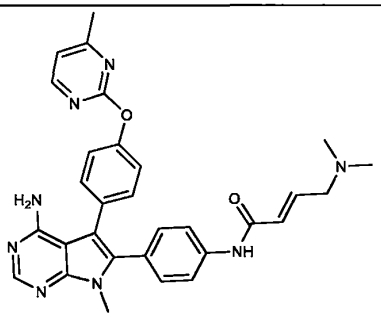
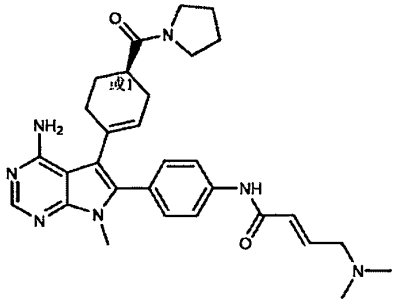
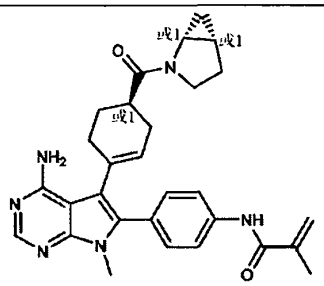
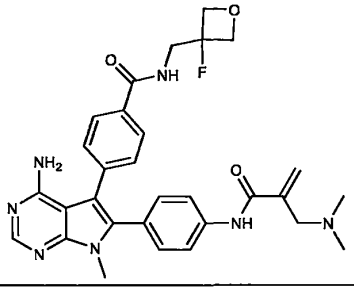
[0624]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1030		A	A
1031		A	B
1032		C	A
1033		A	A
1034		B	A

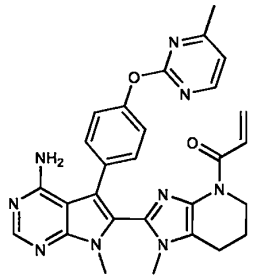
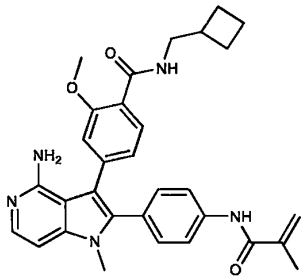
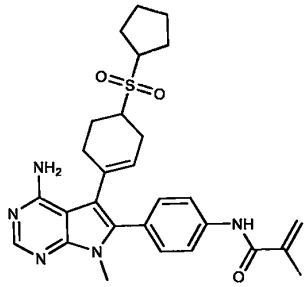
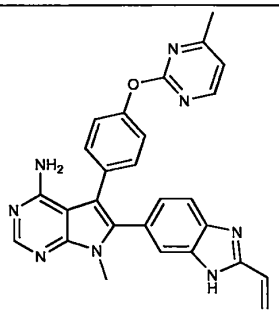
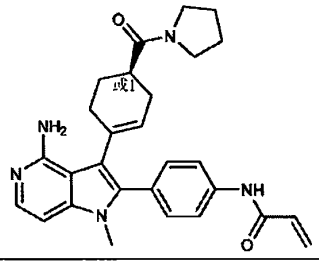
[0625]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1035		A	A
1036		C	A
1037		A	C
1038		A	A
1039		D	D

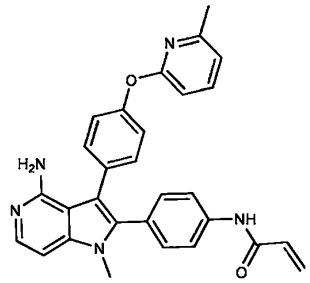
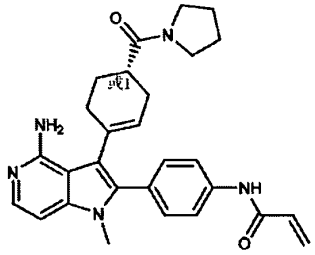
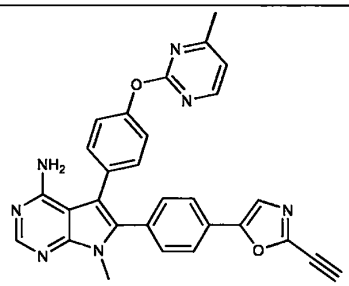
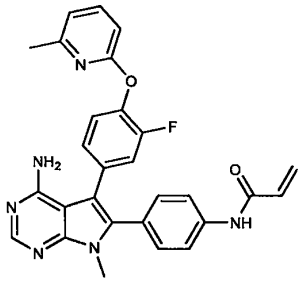
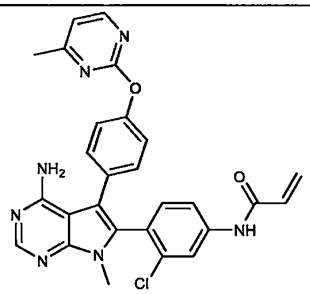
[0626]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1040		D	C
1041		B	A
1042		A	A
1043		A	A
1044		A	A

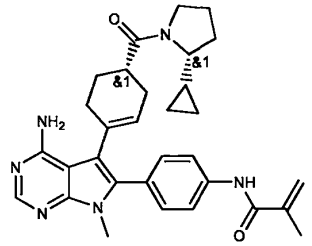
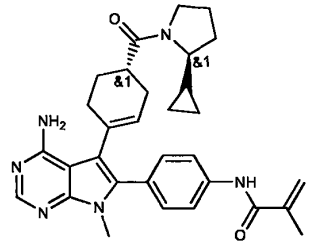
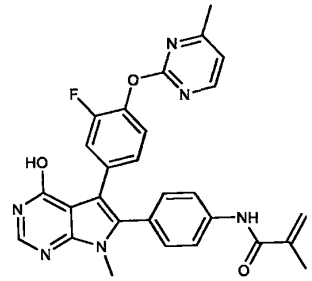
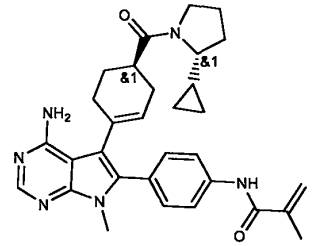
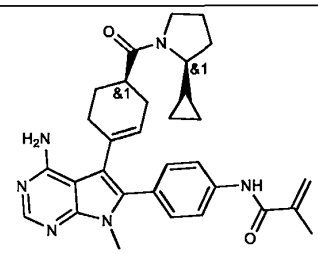
[0627]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1045		D	D
1046		D	D
1047		C	C
1048		C	B
1049		A	A

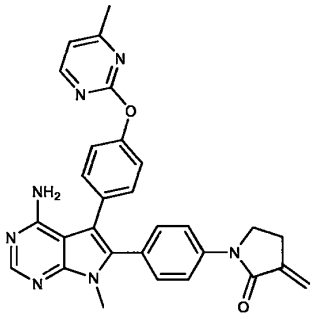
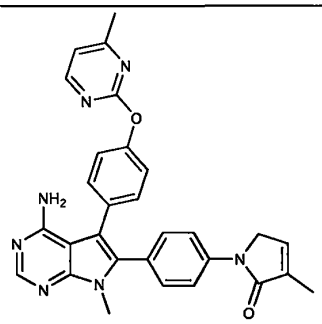
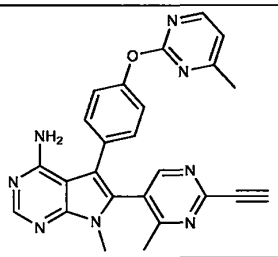
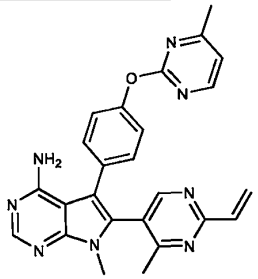
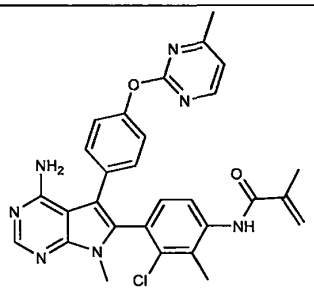
[0628]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1050		C	C
1051		A	A
1052		D	D
1053		B	C
1054		A	A

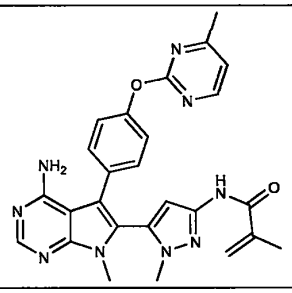
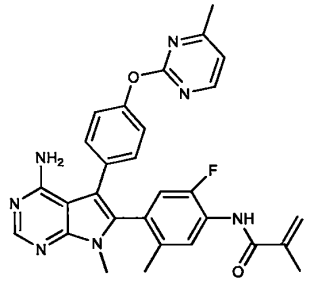
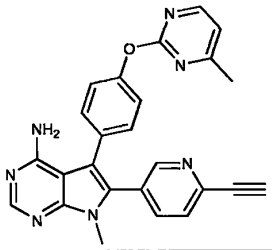
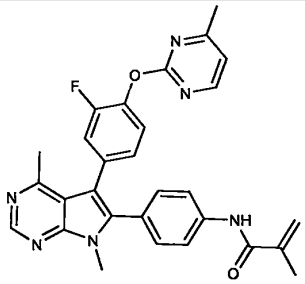
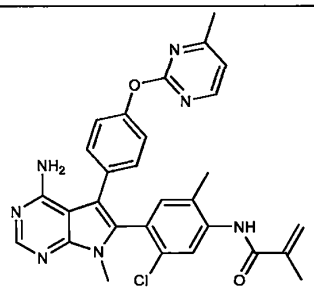
[0629]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1055		A	A
1056		C	A
1057		A	A
1058		D	D
1059		D	D

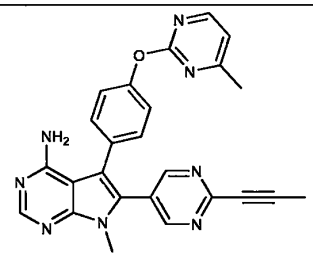
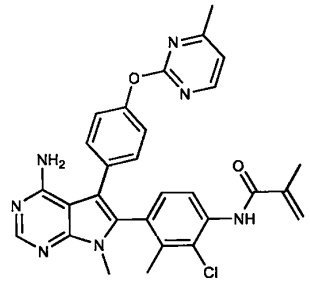
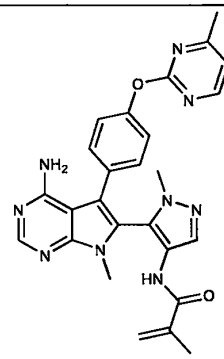
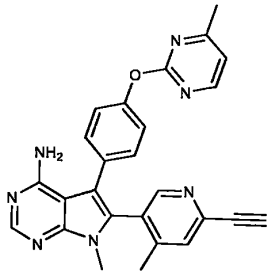
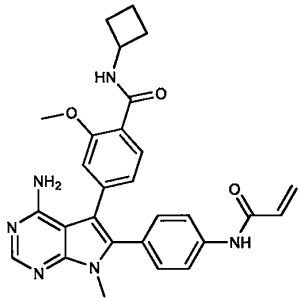
[0630]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1060		D	D
1061		A	A
1062		D	D
1063		A	A
1064		A	A

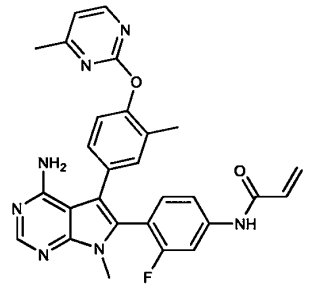
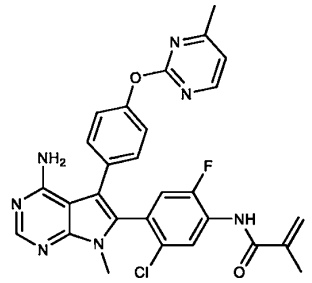
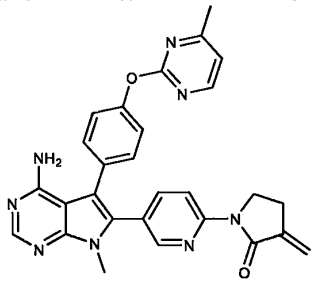
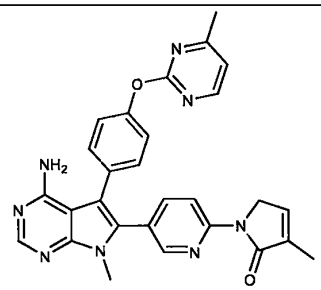
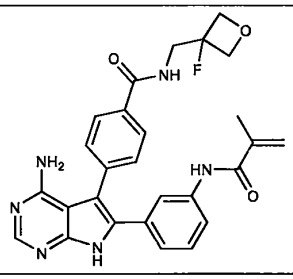
[0631]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1065		C	C
1066		A	A
1067		A	A
1068		A	A
1069		C	C

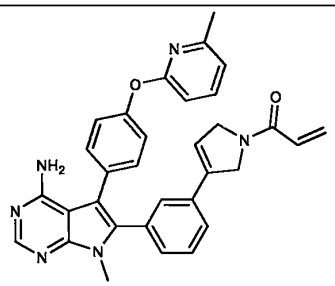
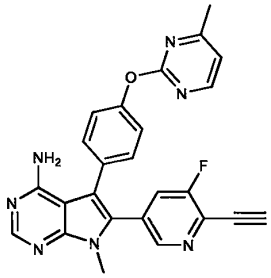
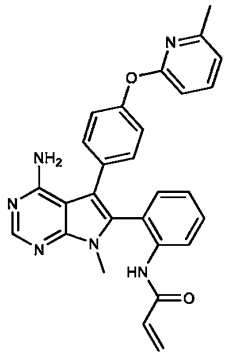
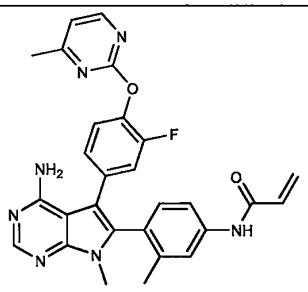
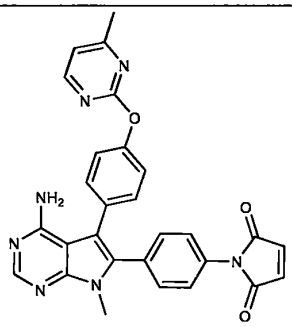
[0632]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1070		A	A
1071		C	A
1072		C	C
1073		D	D
1074		A	A

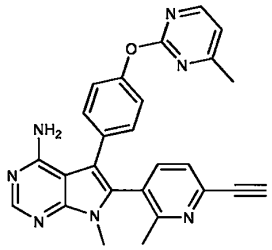
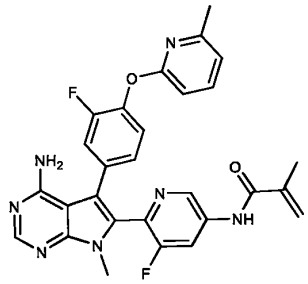
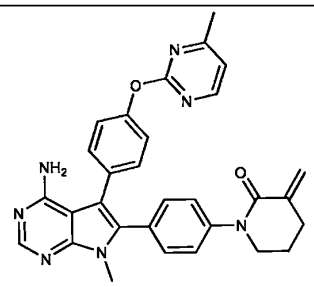
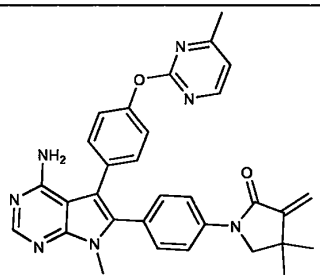
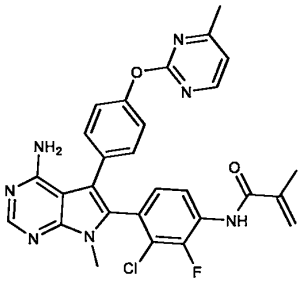
[0633]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1075		A	
1076		A	
1077		A	A
1078		A	A
1079		A	A

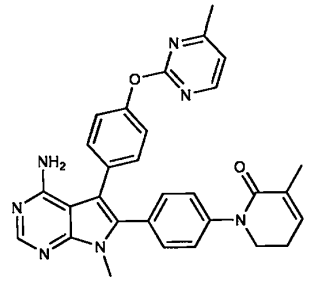
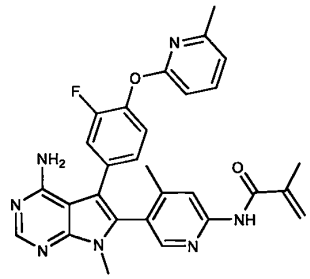
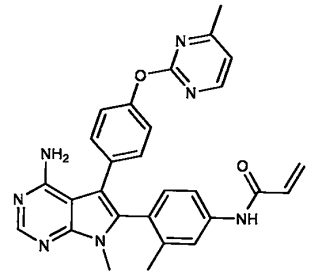
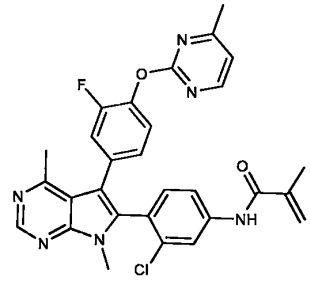
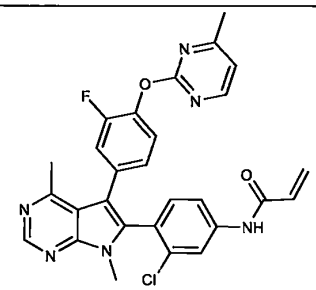
[0634]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1080		D	D
1081		C	C
1082		A	A
1083		C	D
1084		A	A

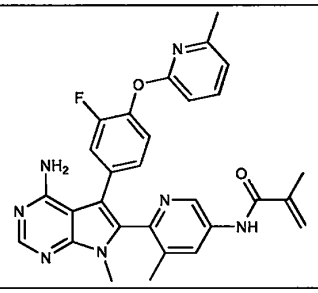
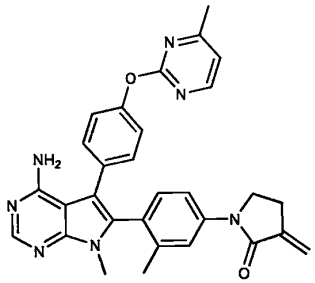
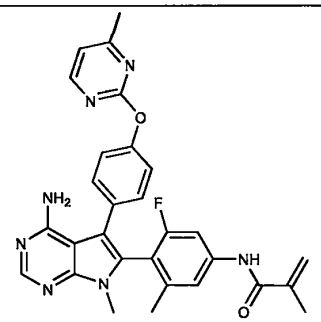
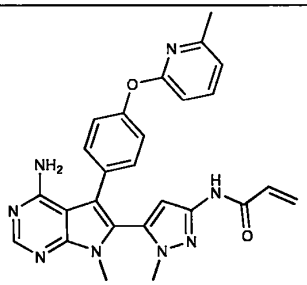
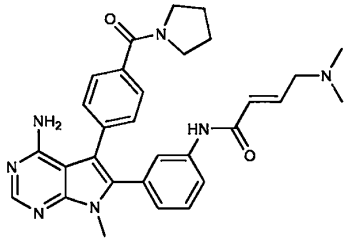
[0635]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1085		D	D
1086		A	A
1087		A	A
1088		D	C
1089		D	D

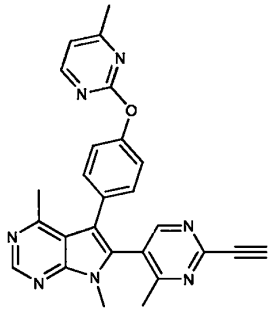
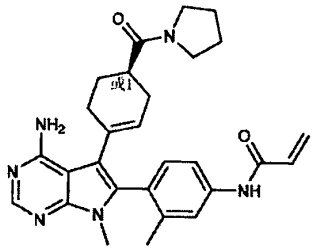
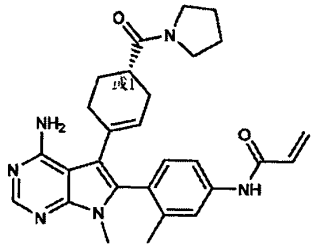
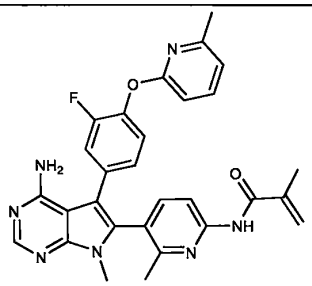
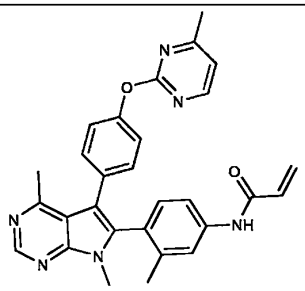
[0636]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1090		A	A
1091		D	D
1092		A	A
1093		A	A
1094		A	A

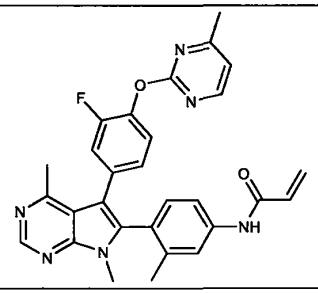
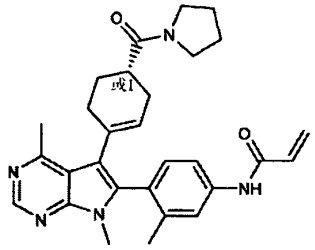
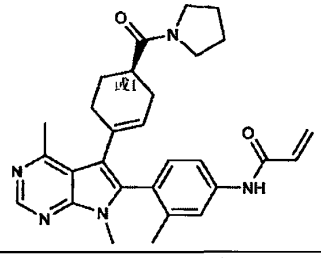
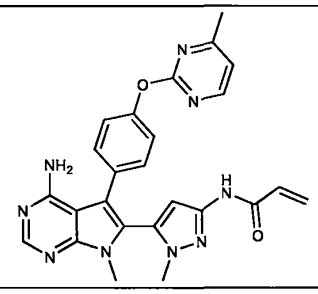
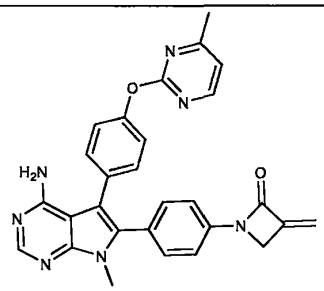
[0637]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1095		A	A
1096		A	A
1097		A	A
1098		A	A
1099		A	

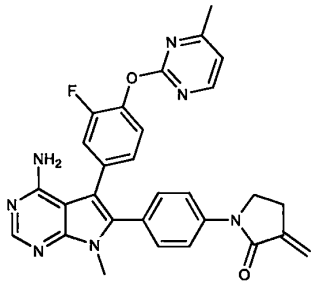
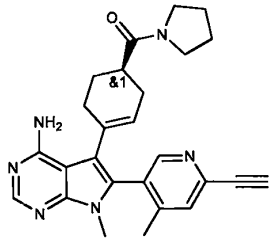
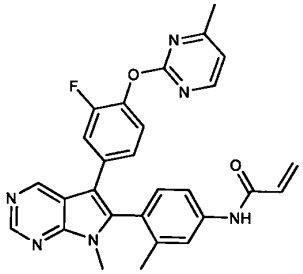
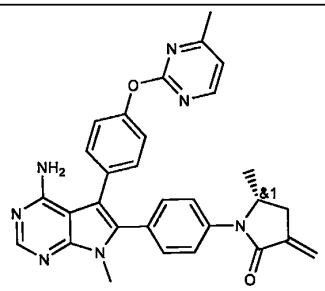
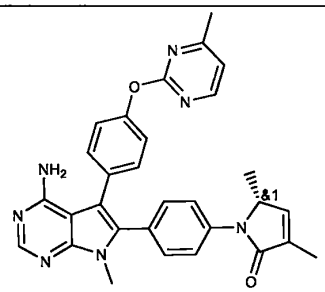
[0638]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1100		B	
1101		A	
1102		A	A
1103		A	A
1104		A	A

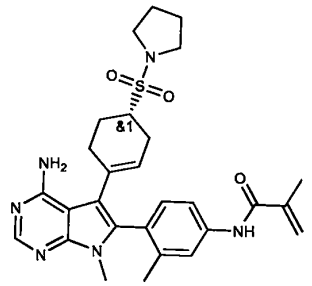
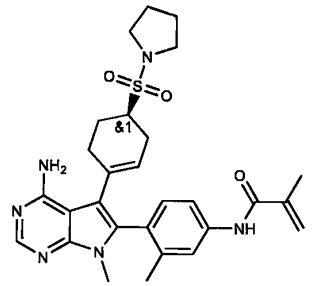
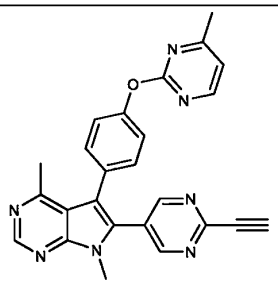
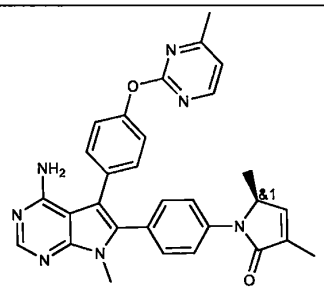
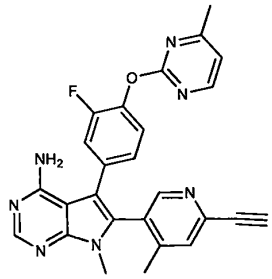
[0639]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1105		A	A
1106		A	A
1107		A	A
1108		A	A
1109		A	A

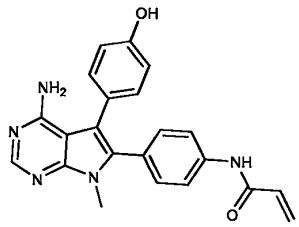
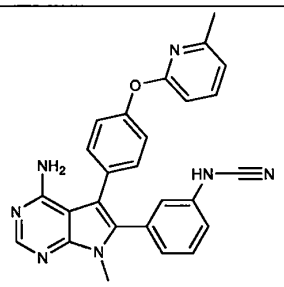
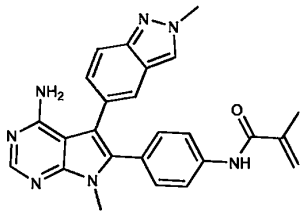
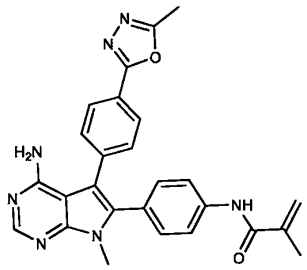
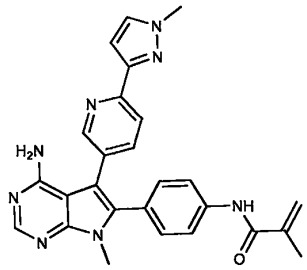
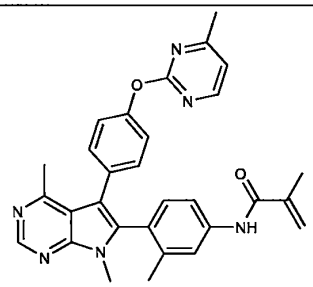
[0640]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1110		A	A
1111		A	A
1112		A	A
1113		A	A
1114		C	A

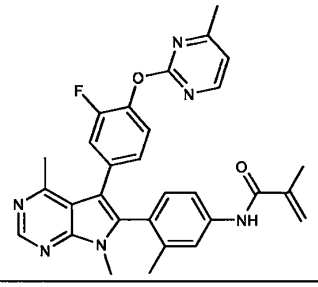
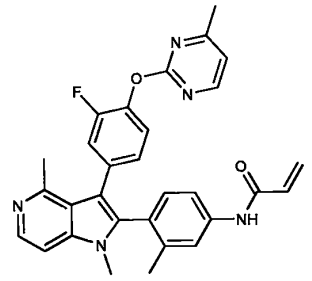
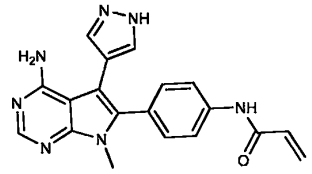
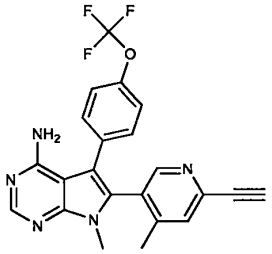
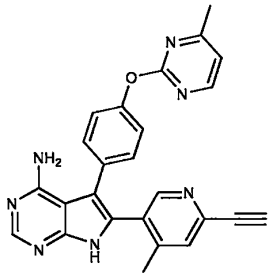
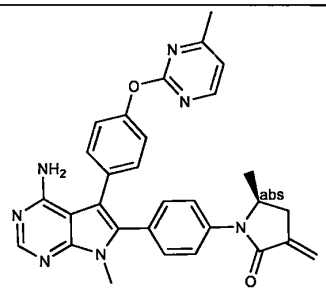
[0641]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1115		D	D
1116		B	A
1117		B	A
1118		A	A
1119		D	C

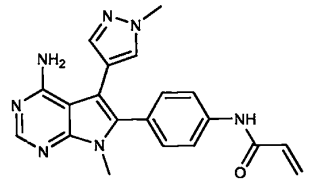
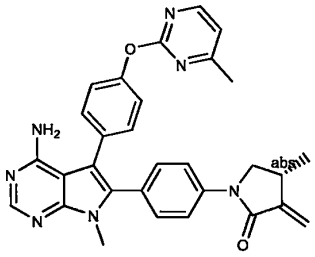
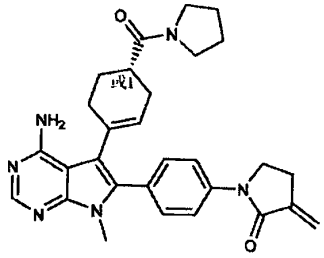
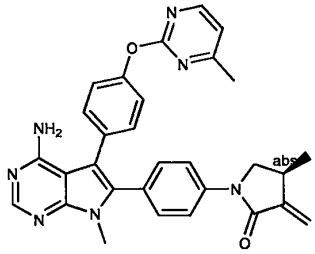
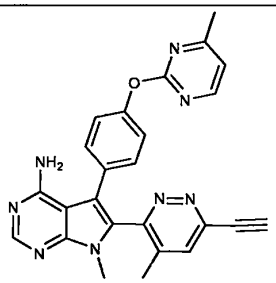
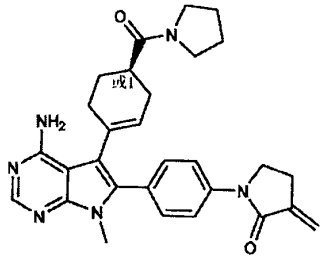
[0642]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1120		A	A
1121		A	A
1122		A	
1123		D	C
1124		D	C
1125		D	D

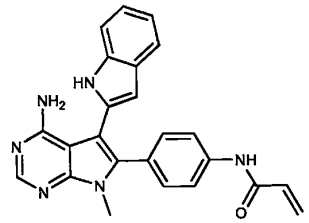
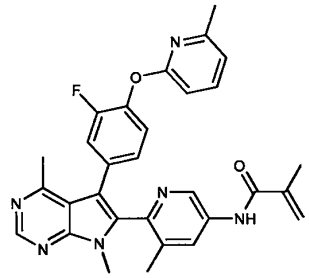
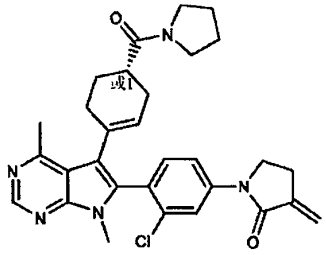
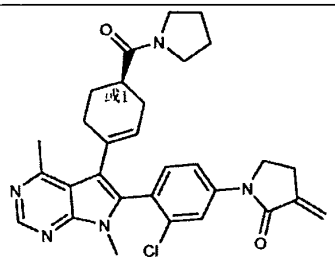
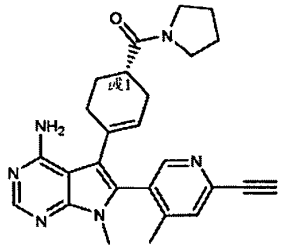
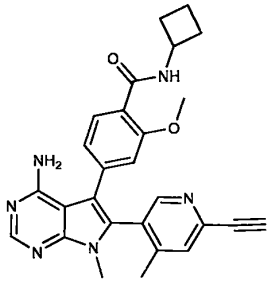
[0643]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1126		A	A
1127		A	A
1128		A	A
1129		A	
1130		C	C
1131		A	A

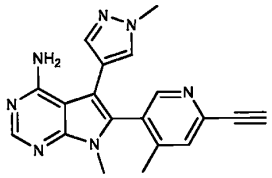
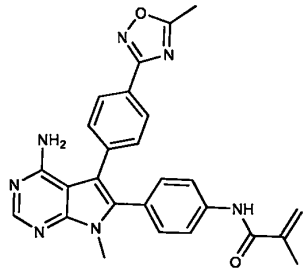
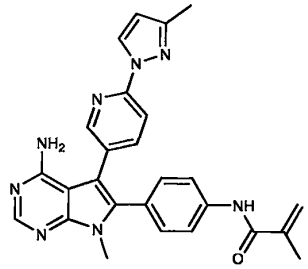
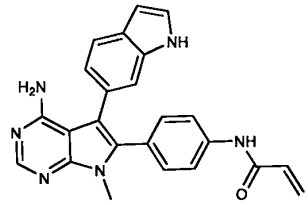
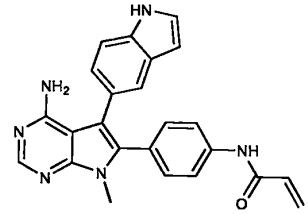
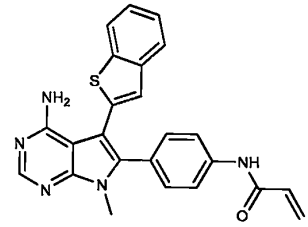
[0644]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1132		D	C
1133		B	B
1134		C	B
1135		C	B
1136		A	A
1137		C	B

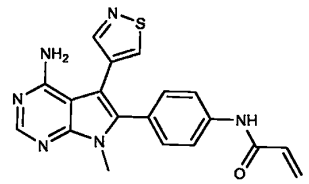
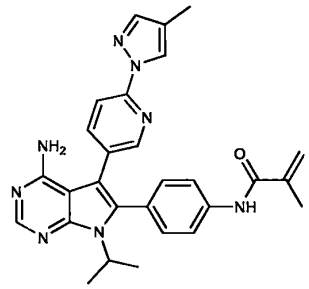
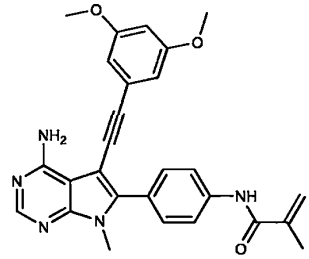
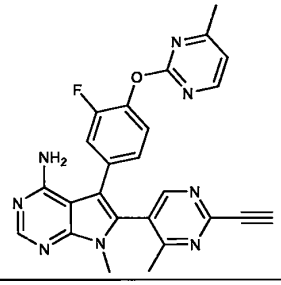
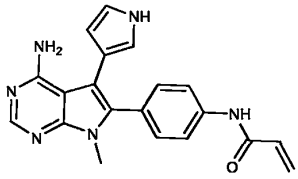
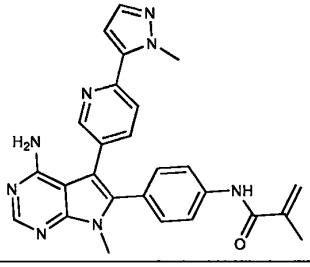
[0645]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1138		A	A
1139		A	
1140		A	A
1141		A	A
1142		A	A
1143		D	C

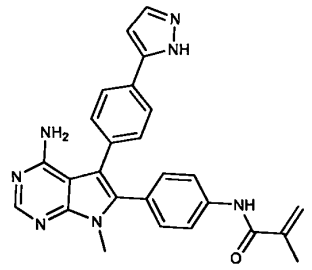
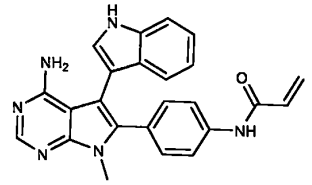
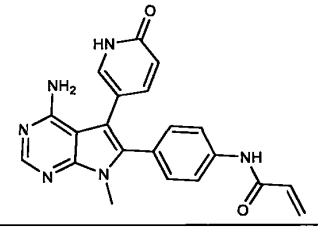
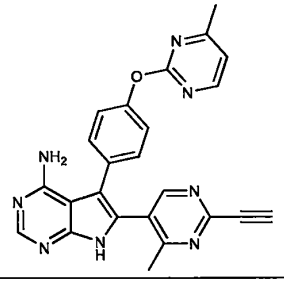
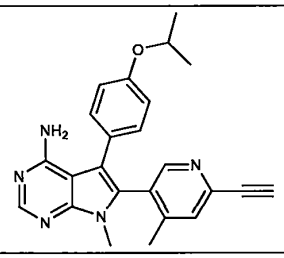
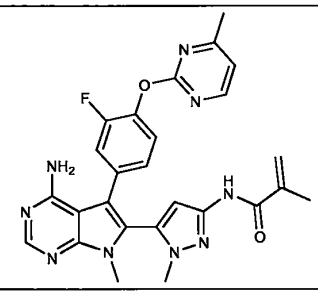
[0646]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1144		B	A
1145		D	D
1146		C	
1147		D	
1148		A	A
1149		A	

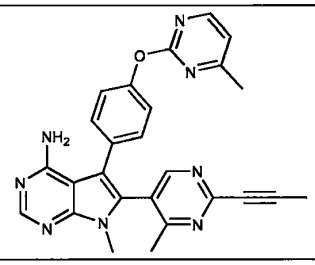
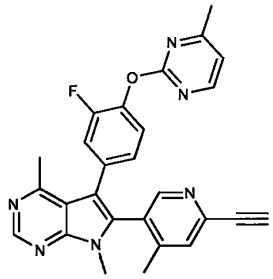
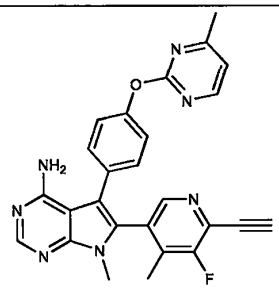
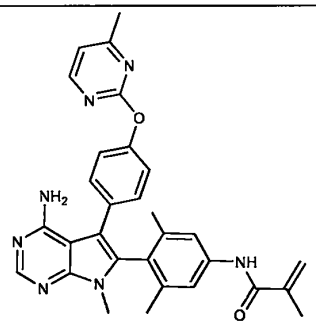
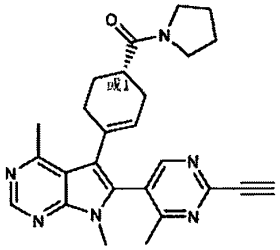
[0647]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1150		A	
1151		B	C
1152		D	
1153		A	B
1154		A	A
1155		A	A

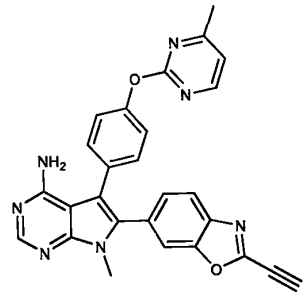
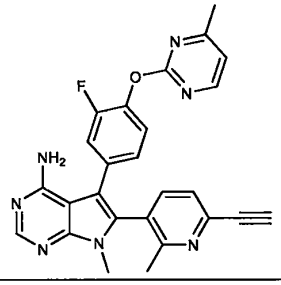
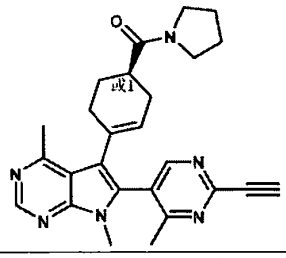
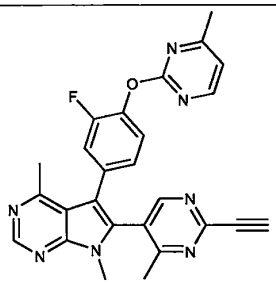
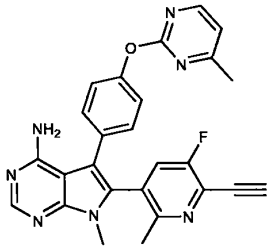
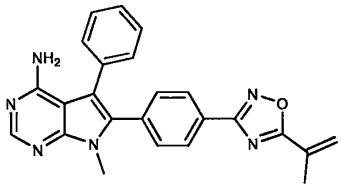
[0648]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1156		D	
1157		C	C
1158		A	A
1159		C	
1160		A	A
1161		A	A

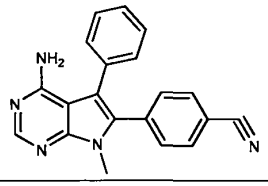
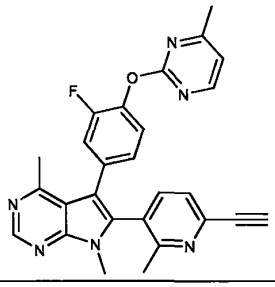
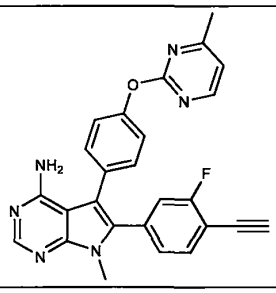
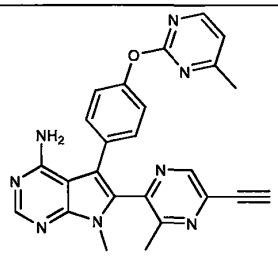
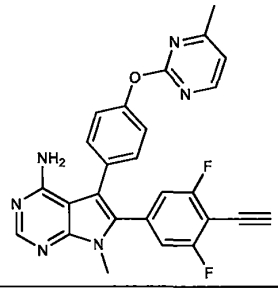
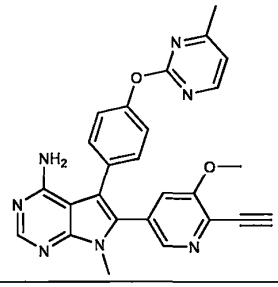
[0649]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1162		A	A
1163		A	A
1164		A	A
1165		A	A
1166		A	A

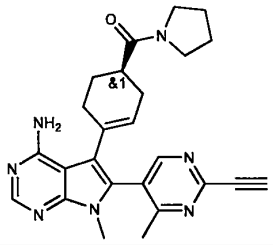
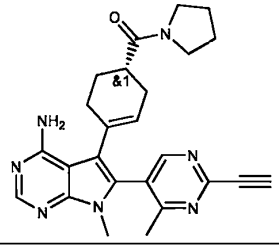
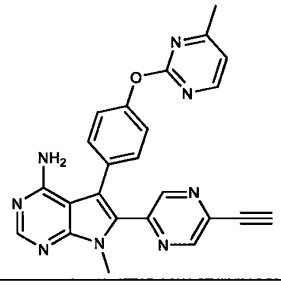
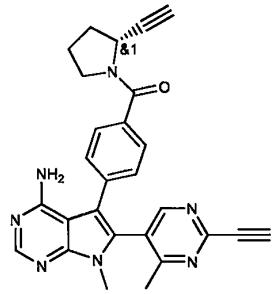
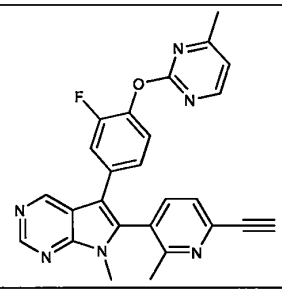
[0650]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1167		A	A
1168		A	D
1169		A	A
1170		A	A
1171		A	A
1172		A	A

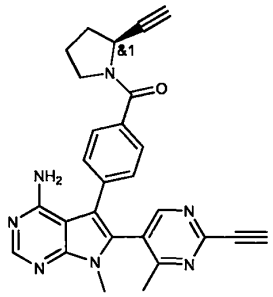
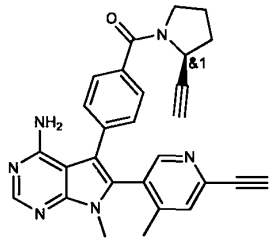
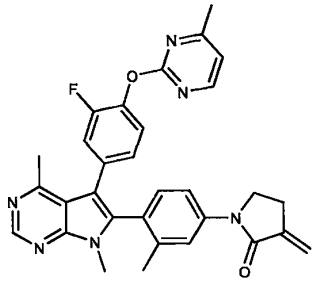
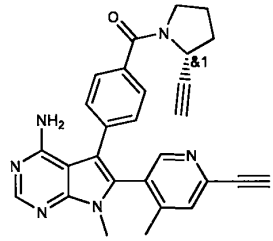
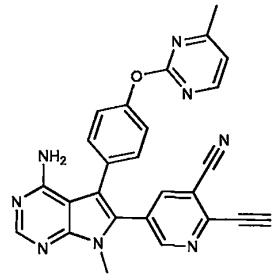
[0651]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1173		D	
1174		D	
1175		B	A
1176		D	
1177		A	A
1178		D	

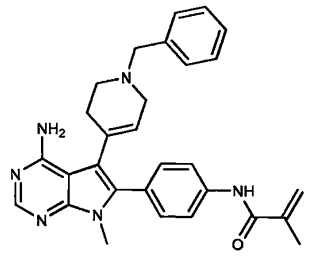
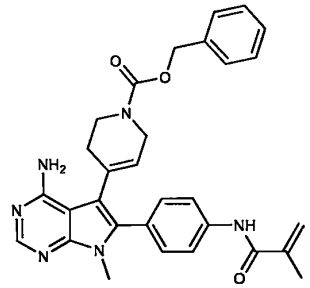
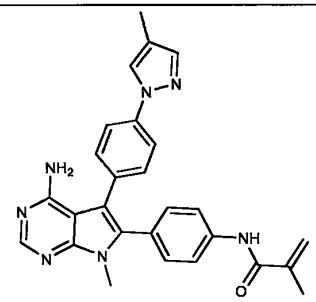
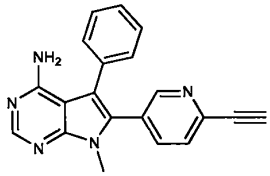
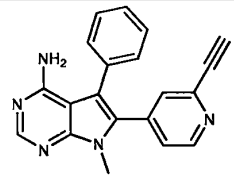
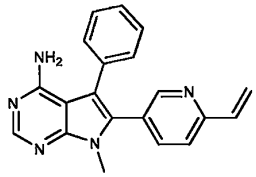
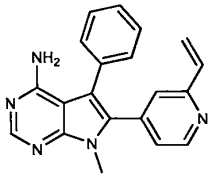
[0652]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1179		A	A
1180		A	A
1181		A	A
1182		A	A
1183		A	A

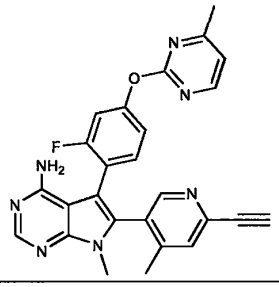
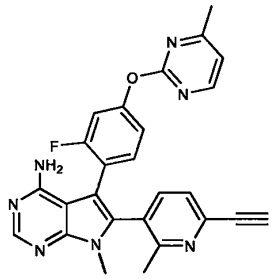
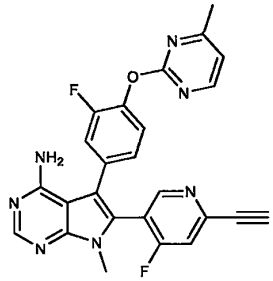
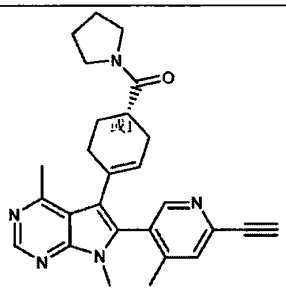
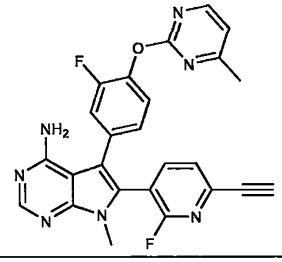
[0653]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1184		D	D
1185		A	A
1186		A	A
1187		A	A
1188		A	A

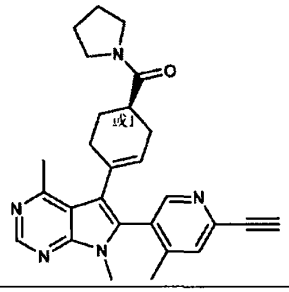
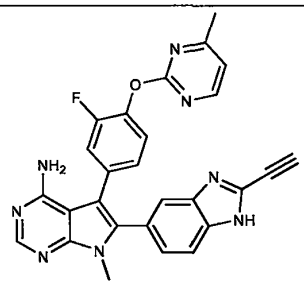
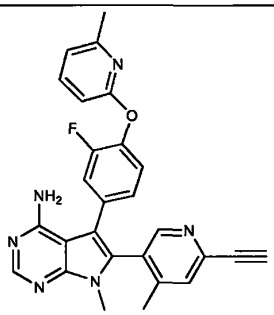
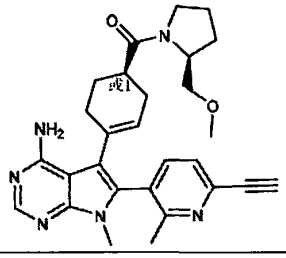
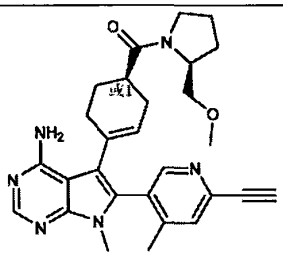
[0654]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1189		A	A
1190		D	
1191		D	
1192		A	
1193		C	C
1194		D	D
1195		B	

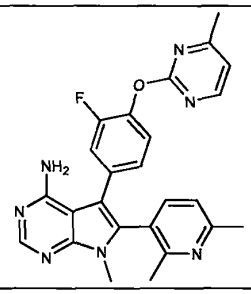
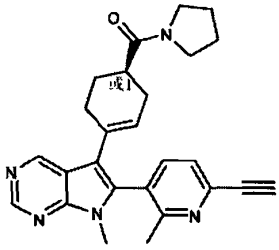
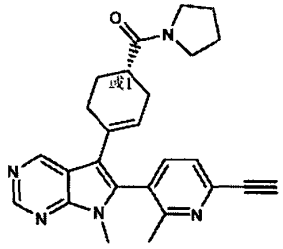
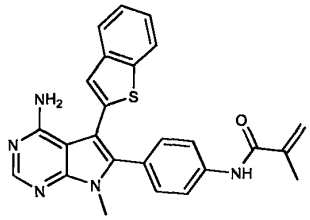
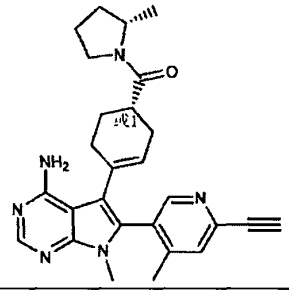
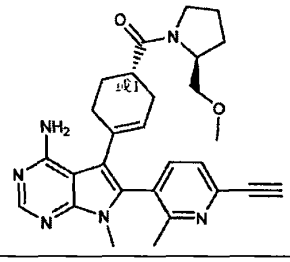
[0655]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1196		C	
1197		A	A
1198		A	A
1199		A	A
1200		D	D

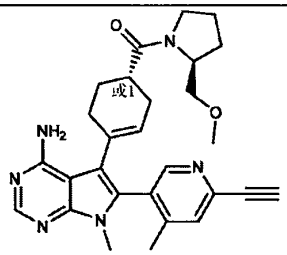
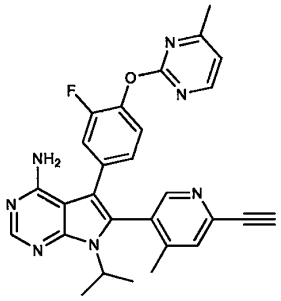
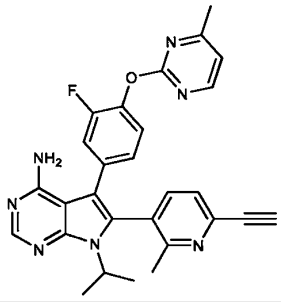
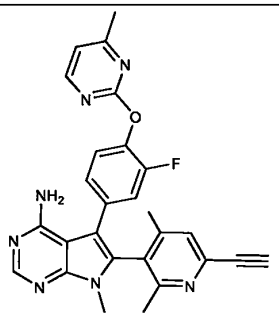
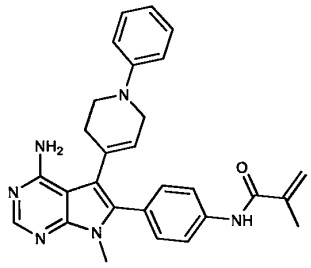
[0656]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1201		A	A
1202		D	C
1203		A	A
1204		A	A
1205		C	C

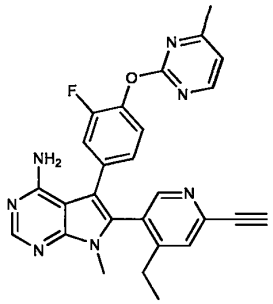
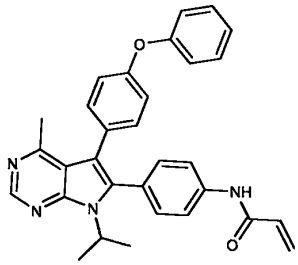
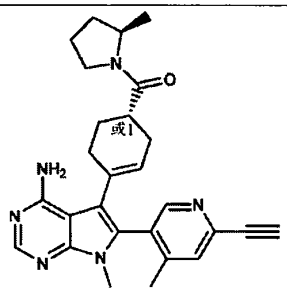
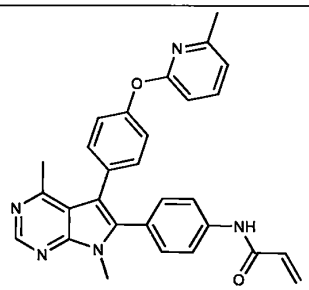
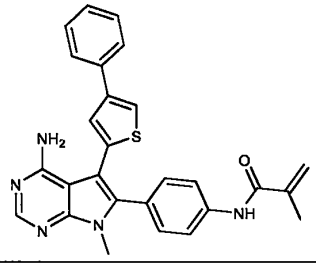
[0657]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1206		C	C
1207		D	D
1208		D	C
1209		C	
1210		A	A
1211		A	B

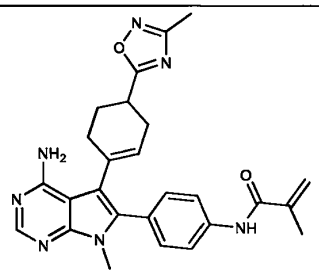
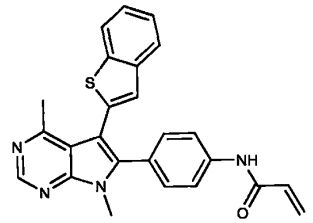
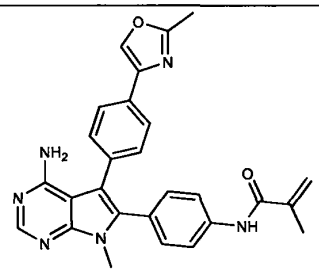
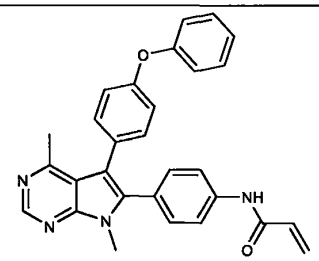
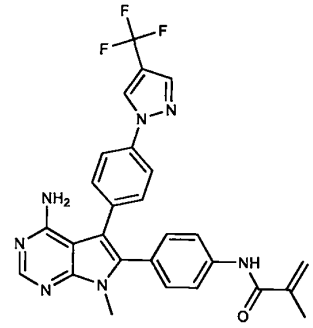
[0658]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1212		A	B
1213		A	A
1214		A	A
1215		A	A
1216		D	

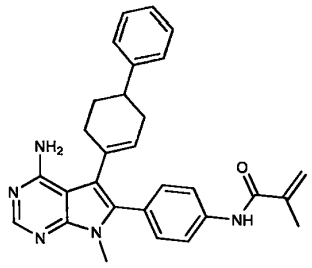
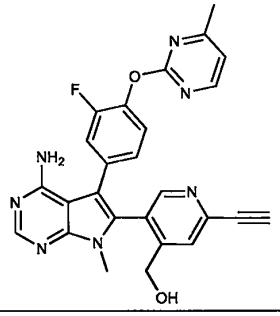
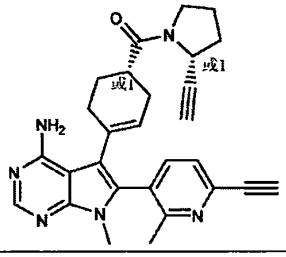
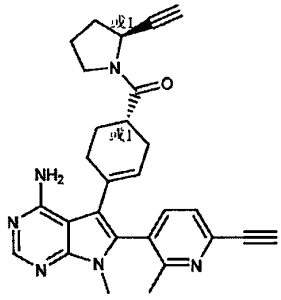
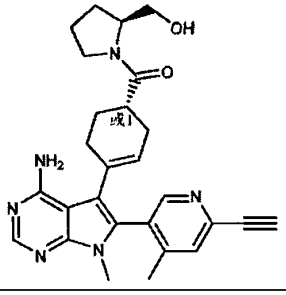
[0659]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1217		A	A
1218		D	
1219		A	A
1220		A	
1221		C	

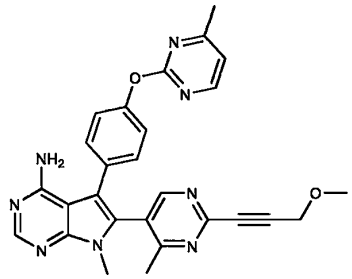
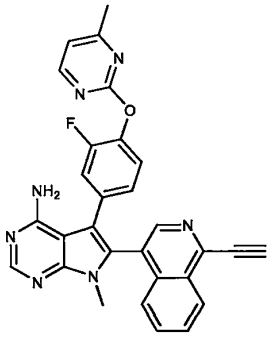
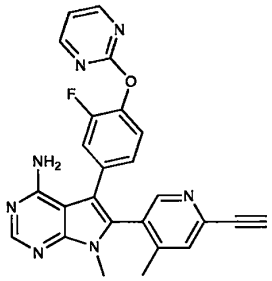
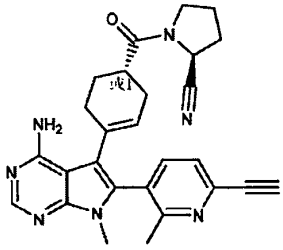
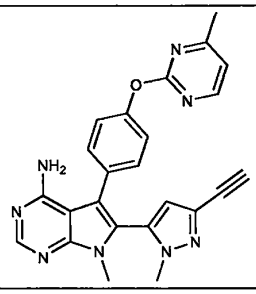
[0660]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1222		D	
1223		D	
1224		C	
1225		C	
1226		D	

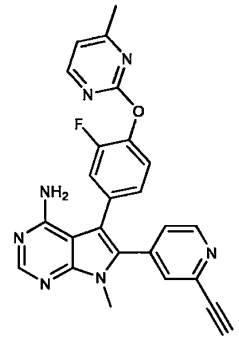
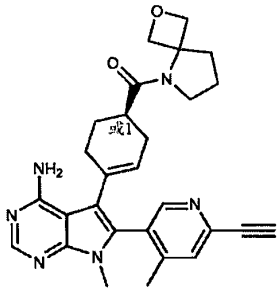
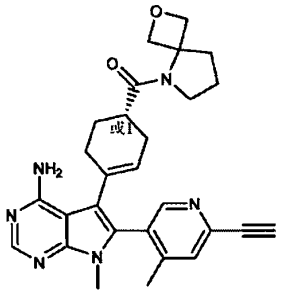
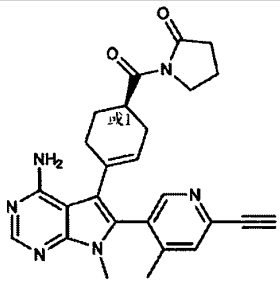
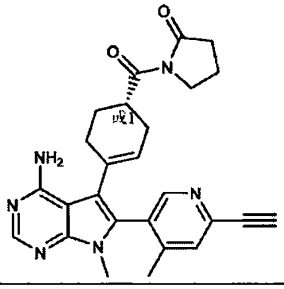
[0661]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1227		D	
1228		A	A
1229		A	A
1230		A	A
1231		A	A

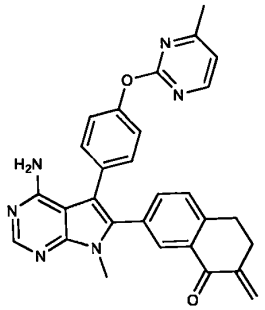
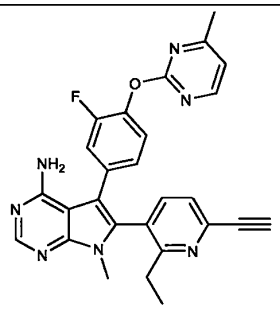
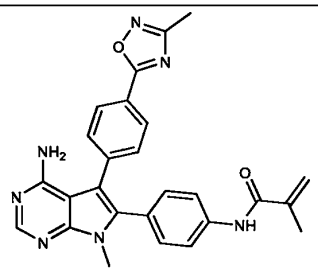
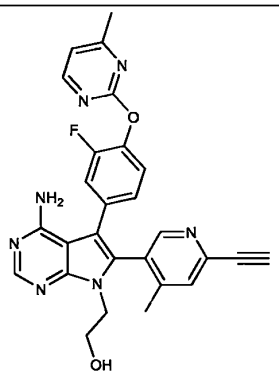
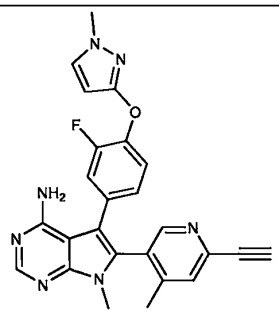
[0662]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1232		A	A
1233		A	A
1234		A	A
1235		A	A
1236		D	D

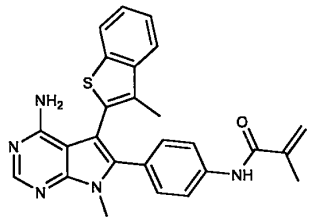
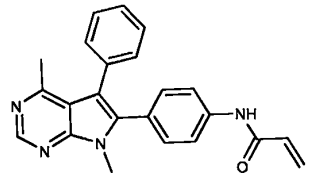
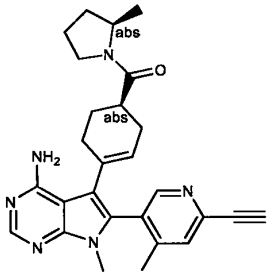
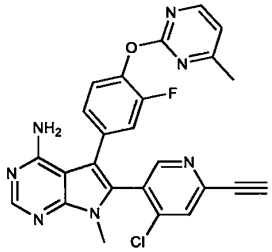
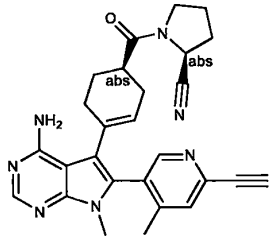
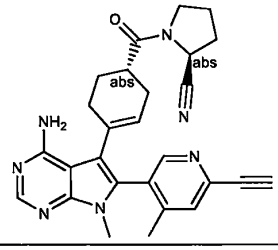
[0663]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1237		C	A
1238		C	B
1239		A	A
1240		B	B
1241		A	A

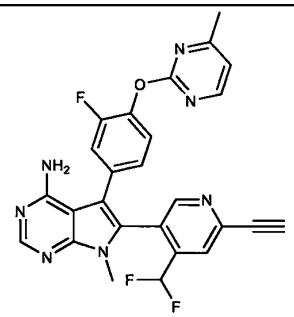
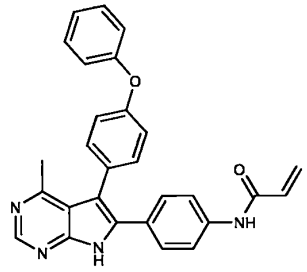
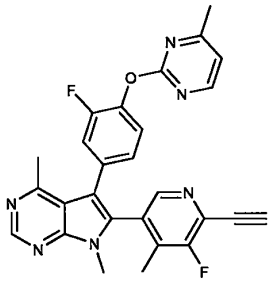
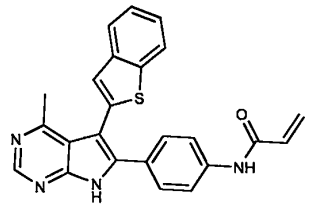
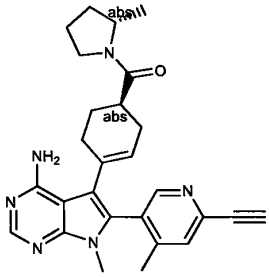
[0664]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1242		B	D
1243		A	A
1244		D	
1245		A	A
1246		A	A

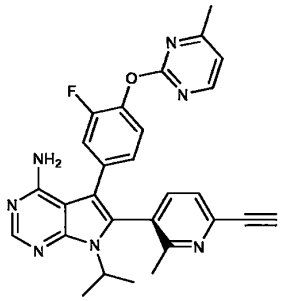
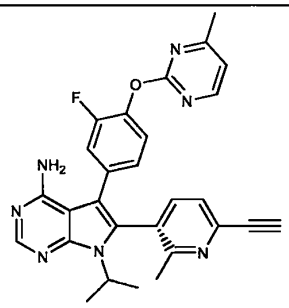
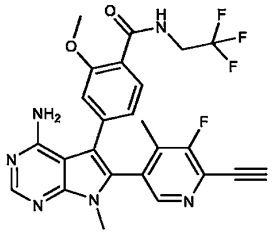
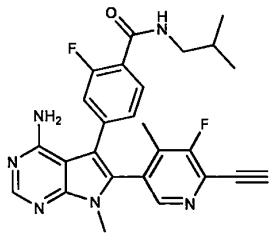
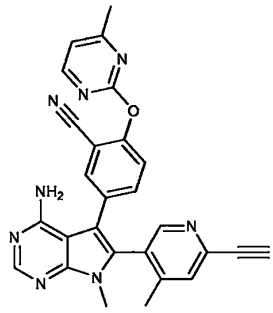
[0665]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1247		D	
1248		D	
1249		C	B
1250		A	A
1251		A	A
1252		A	A

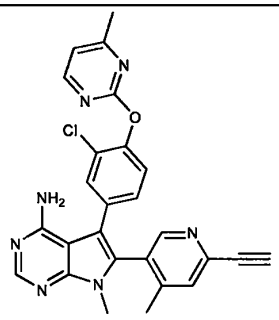
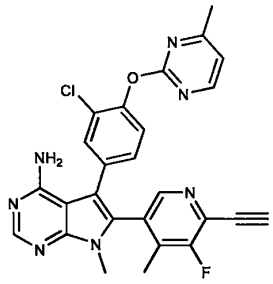
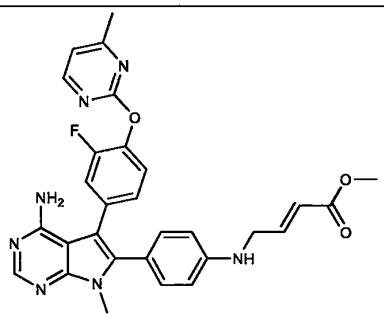
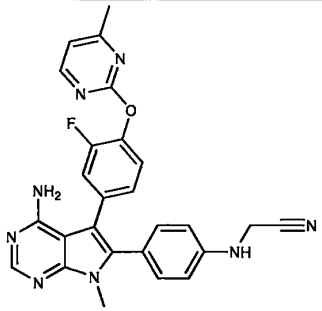
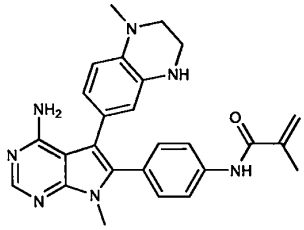
[0666]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1253		A	A
1254		D	
1255		A	A
1256		D	
1257		C	C

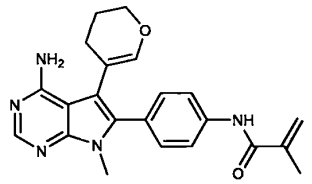
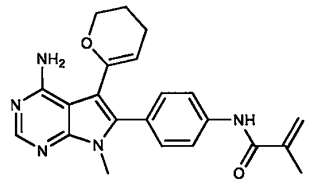
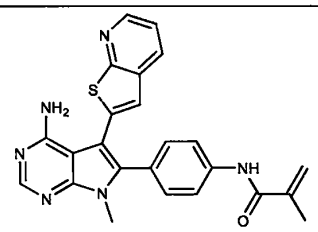
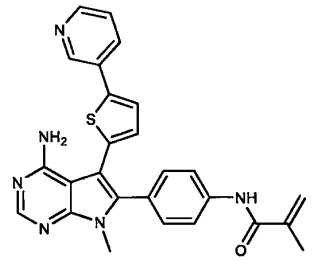
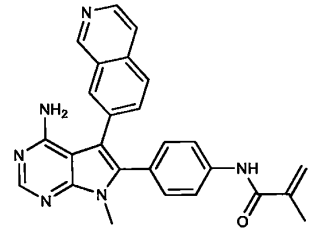
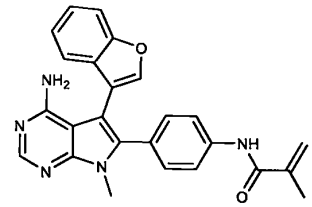
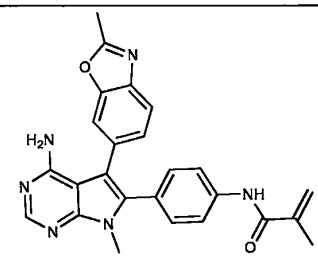
[0667]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1258		A	A
1259		A	A
1260		A	A
1261		A	A
1262		A	A

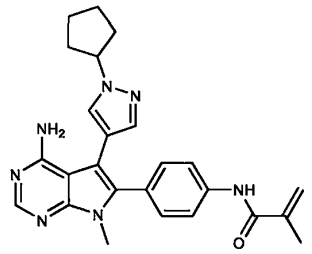
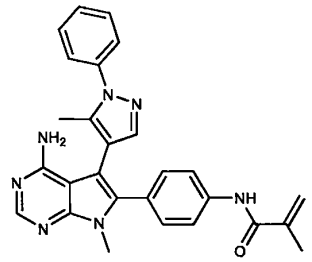
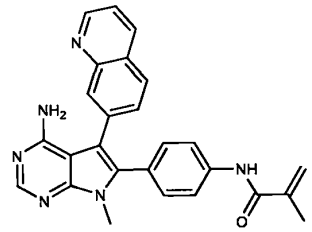
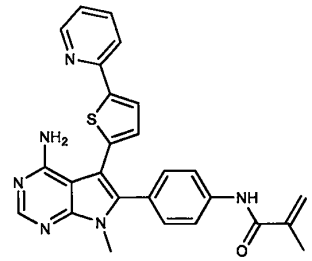
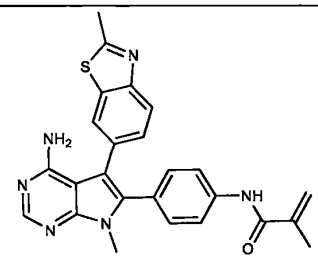
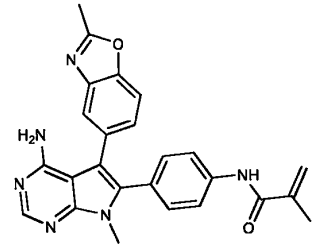
[0668]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1263		A	A
1264		A	A
1265		A	B
1266		D	C
1267		D	D

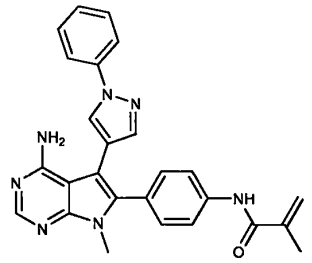
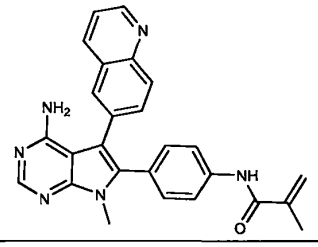
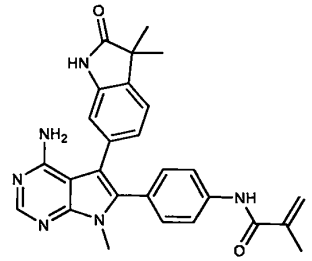
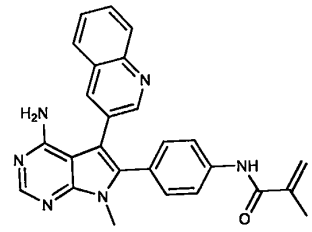
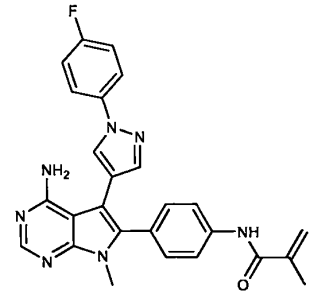
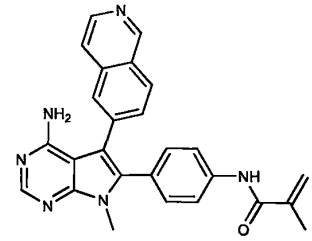
[0669]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1268		D	D
1269		D	D
1270		C	C
1271		D	D
1272		D	D
1273		D	D
1274		D	D

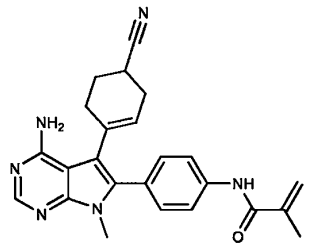
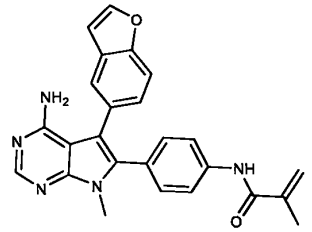
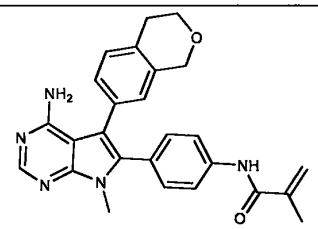
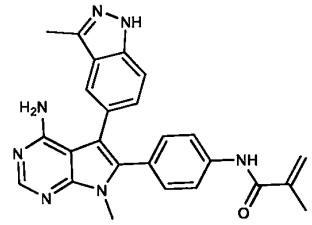
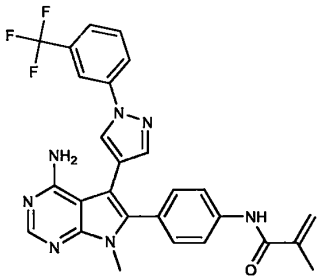
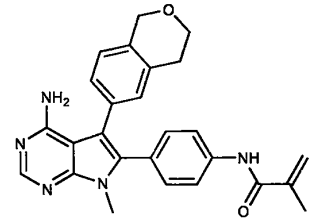
[0670]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1275		C	C
1276		D	D
1277		C	D
1278		C	C
1279		C	C
1280		C	C

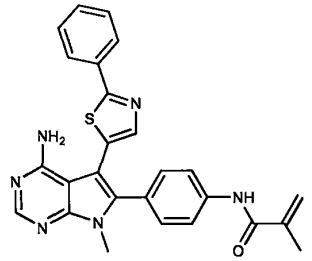
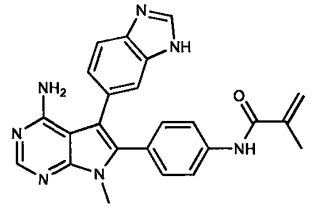
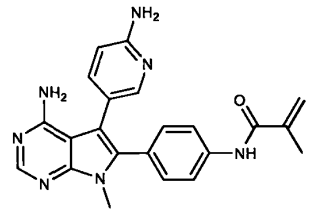
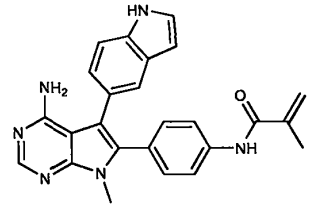
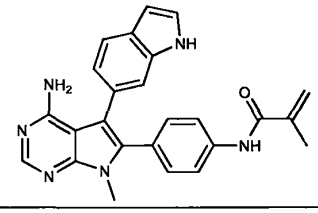
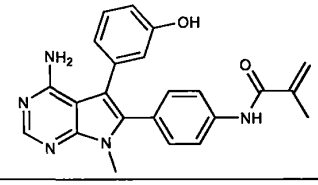
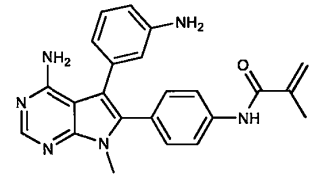
[0671]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1281		D	C
1282		D	D
1283		D	D
1284		D	D
1285		C	D
1286		C	C

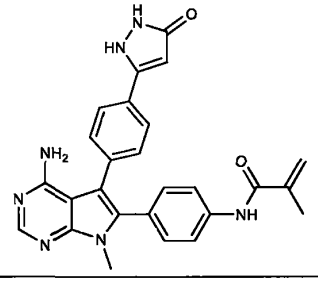
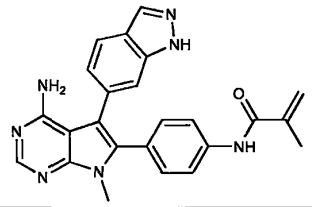
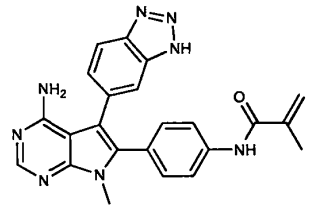
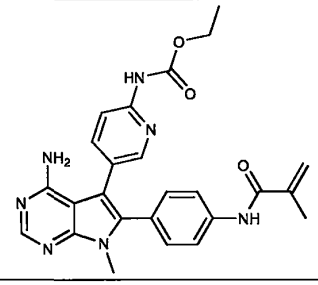
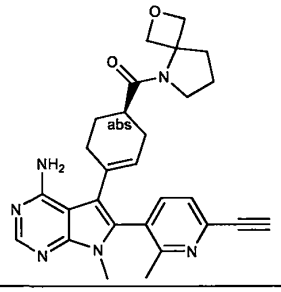
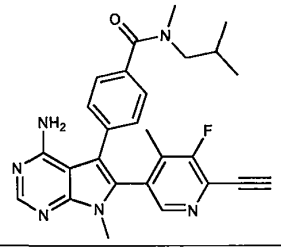
[0672]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1287		D	D
1288		D	D
1289		D	D
1290		D	D
1291		D	D
1292		D	D

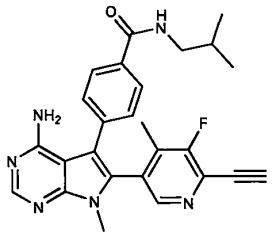
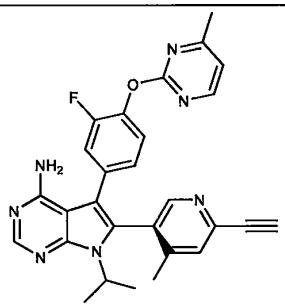
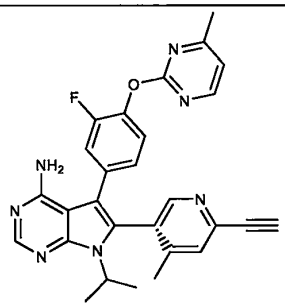
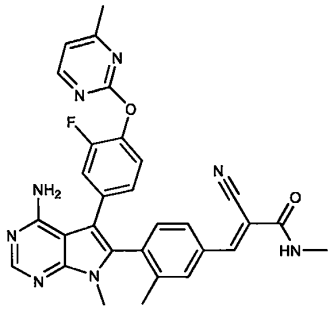
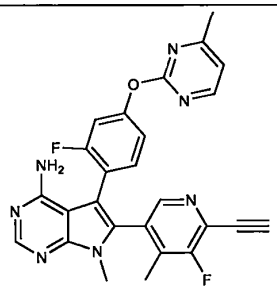
[0673]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1293		B	C
1294		C	D
1295		D	D
1296		B	C
1297		C	C
1298		C	D
1299		D	D

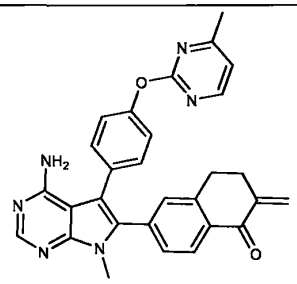
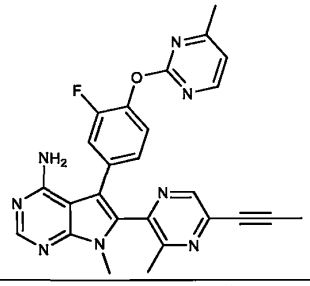
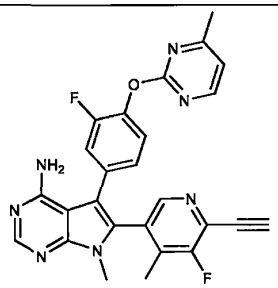
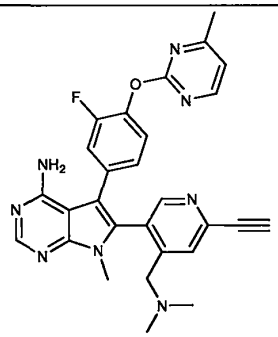
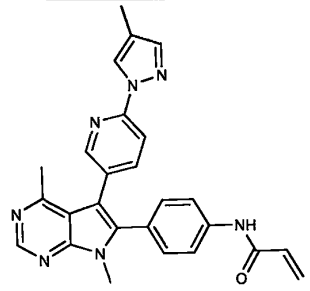
[0674]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1300		D	D
1301		D	D
1302		D	D
1303		D	D
1304		C	C
1305		A	A

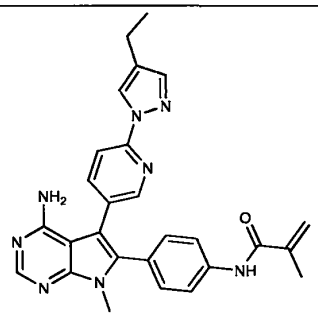
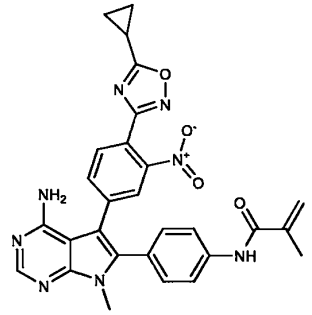
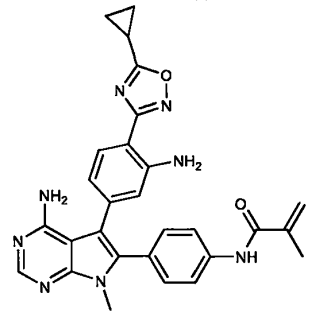
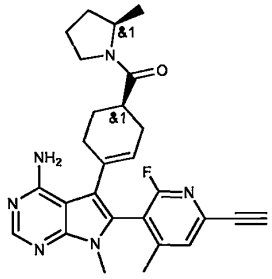
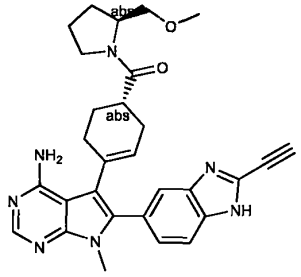
[0675]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1306		A	A
1307		A	A
1308		A	A
1309		A	C
1310		A	A

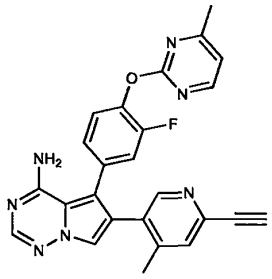
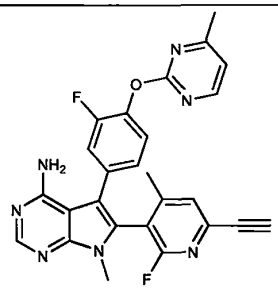
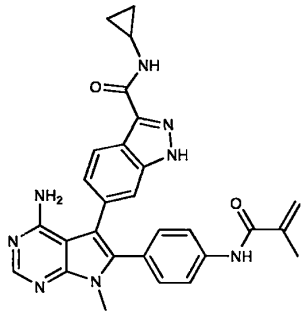
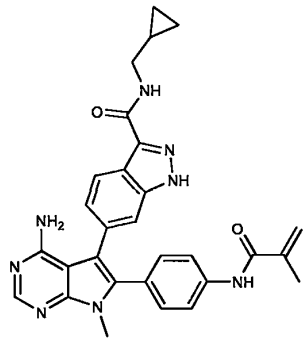
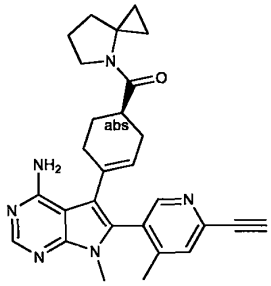
[0676]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1311		A	C
1312		C	B
1313		A	A
1314		B	A
1315		B	C

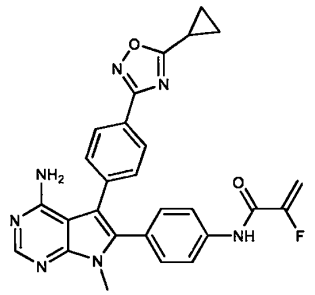
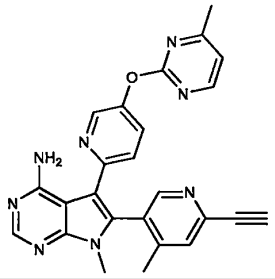
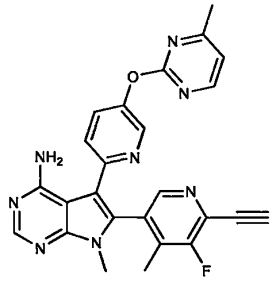
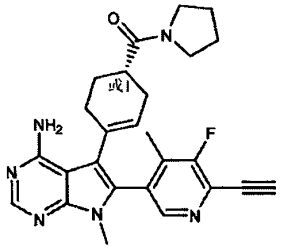
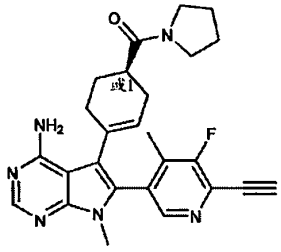
[0677]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1316		C	C
1317		D	
1318		D	
1319		A	A
1320		A	C

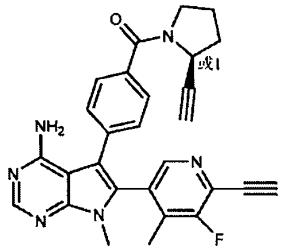
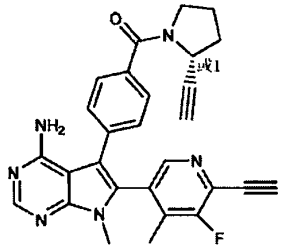
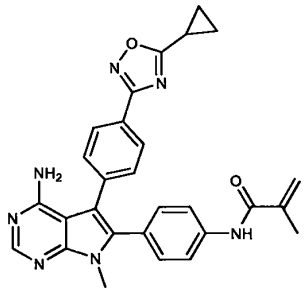
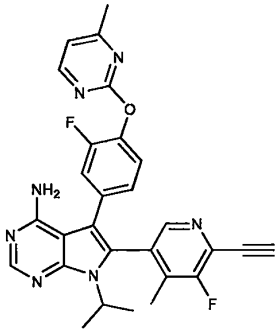
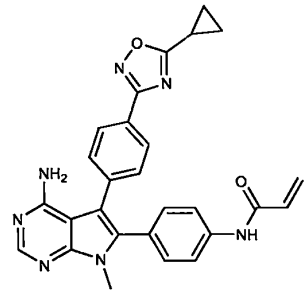
[0678]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1321		A	A
1322		A	A
1323		D	D
1324		D	D
1325		C	C

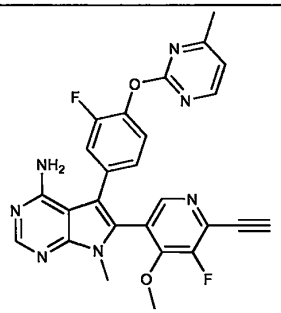
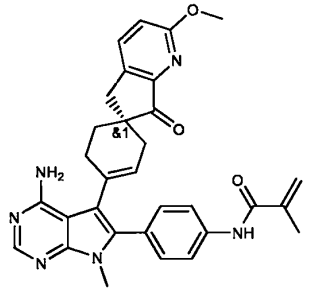
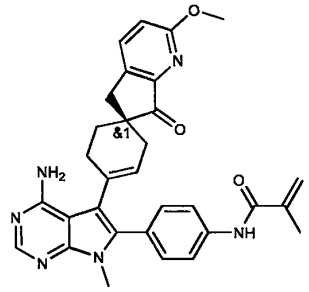
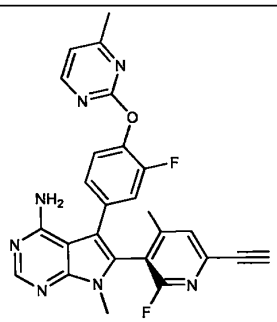
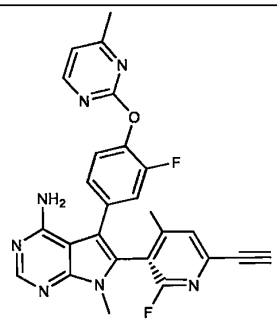
[0679]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1326		B	
1327		A	A
1328		A	A
1329		C	B
1330		A	A

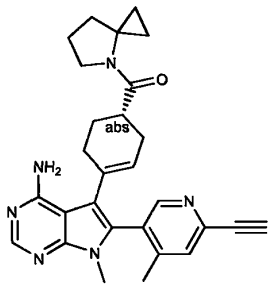
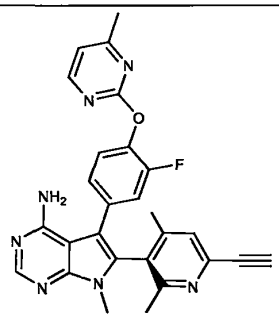
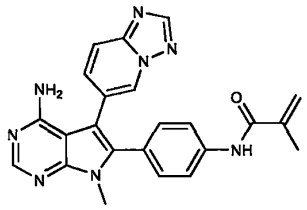
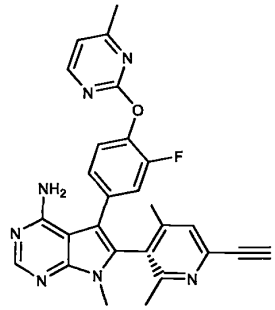
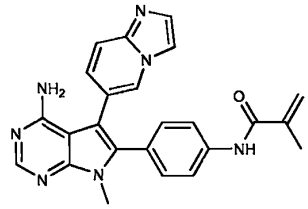
[0680]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1331		A	A
1332		A	A
1333		C	
1334		A	A
1335		A	

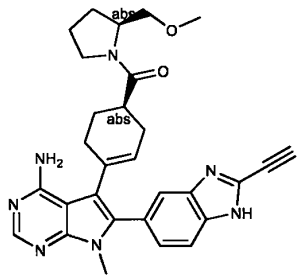
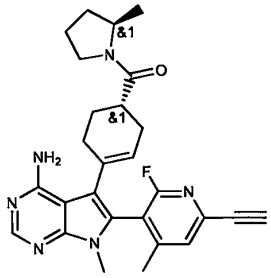
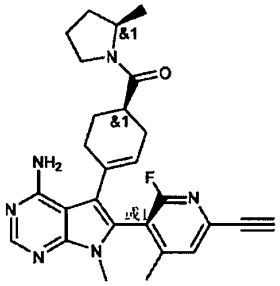
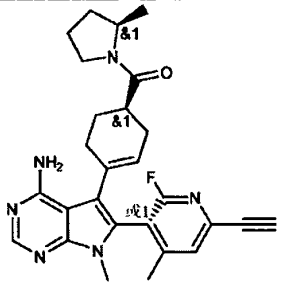
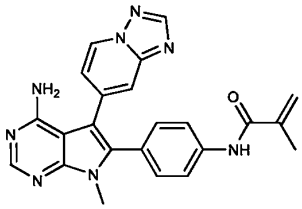
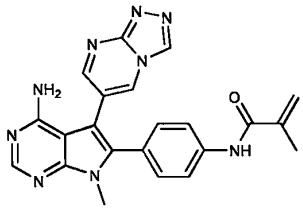
[0681]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1336		A	A
1337		B	A
1338		D	D
1339		A	A
1340		A	A

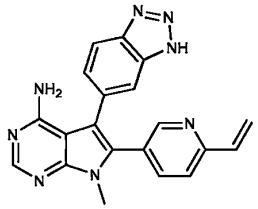
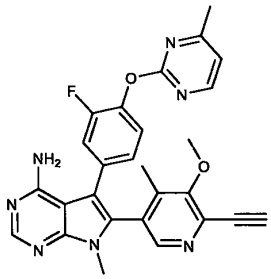
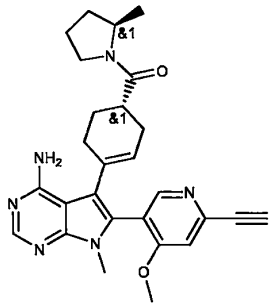
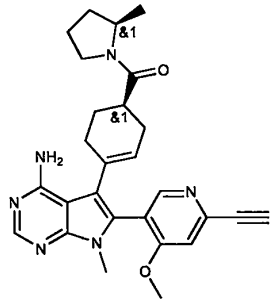
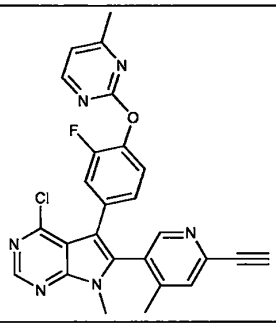
[0682]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1341		A	C
1342		A	A
1343		D	D
1344		A	A
1345		D	D

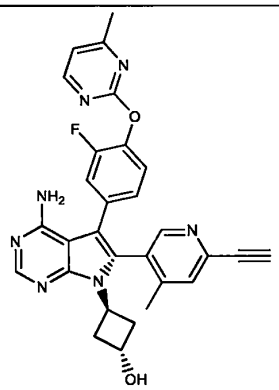
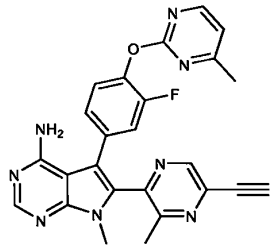
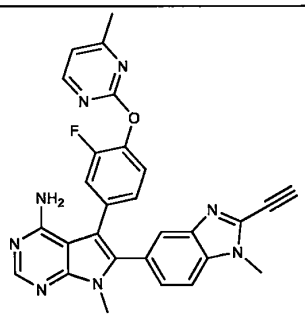
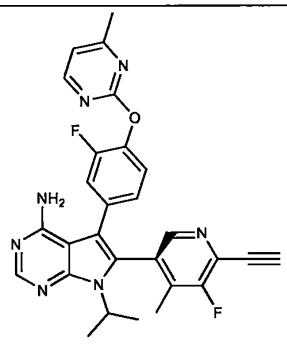
[0683]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1346		A	C
1347		A	A
1348		B	A
1349		A	A
1350		D	D
1351		D	D

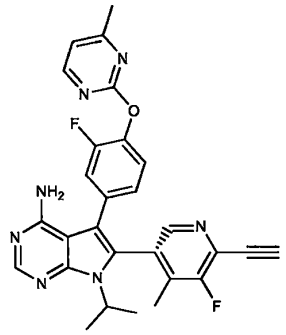
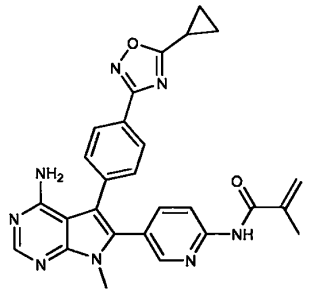
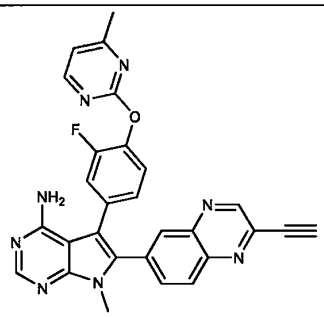
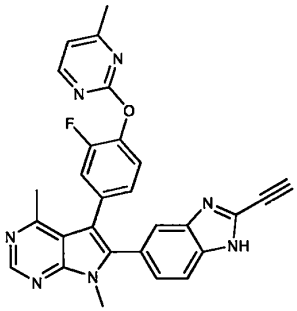
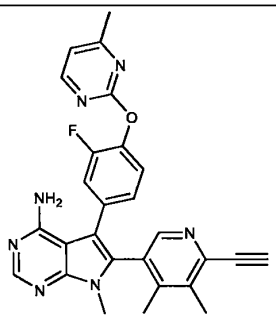
[0684]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1352		A	A
1353		A	A
1354		A	A
1355		A	A
1356		A	A

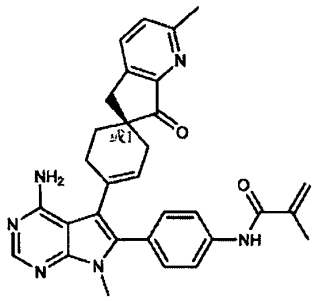
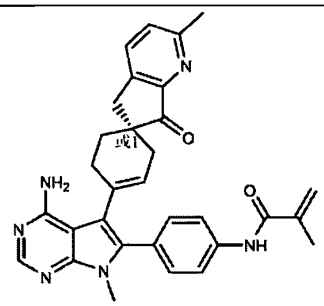
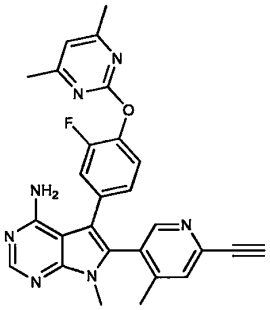
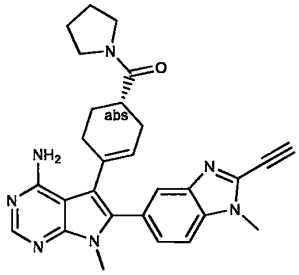
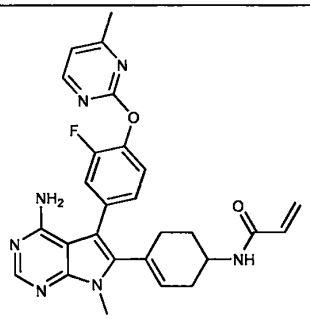
[0685]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1357		A	A
1358		A	A
1359		A	A
1360		A	A

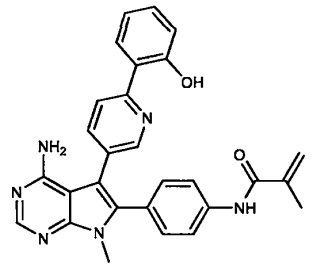
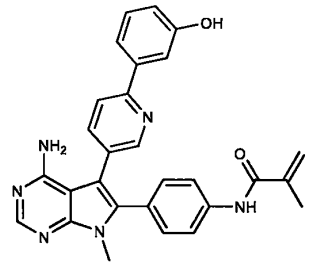
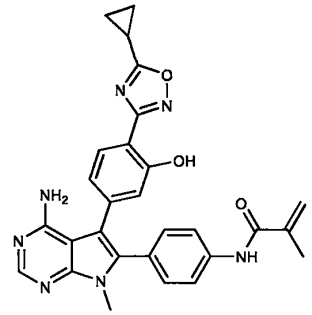
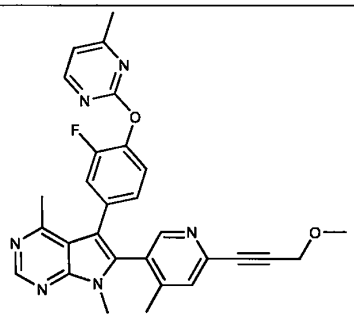
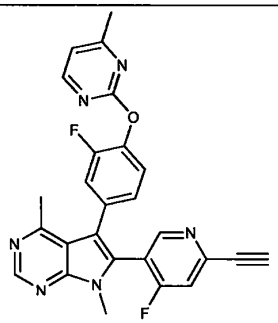
[0686]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1361		A	A
1362		B	
1363		A	A
1364		A	A
1365		A	A

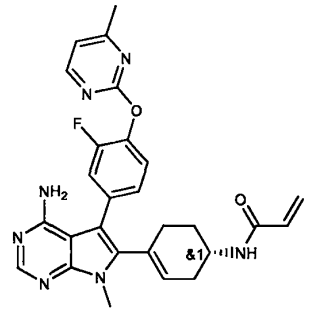
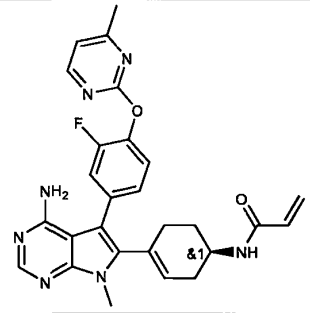
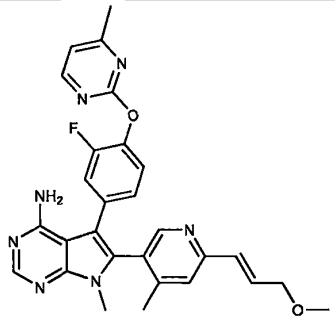
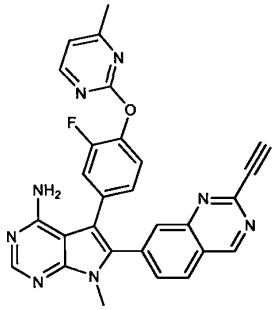
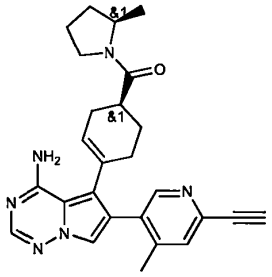
[0687]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1366		D	D
1367		A	A
1368		A	A
1369		A	A
1370		B	B

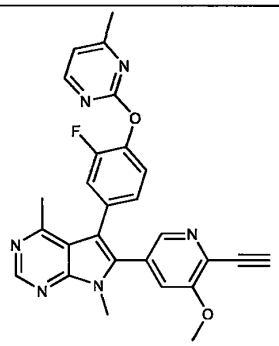
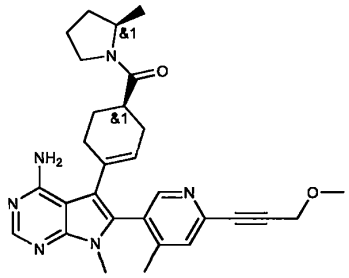
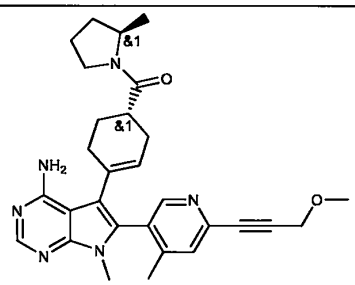
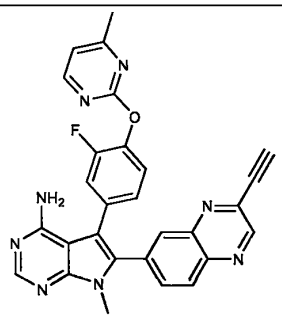
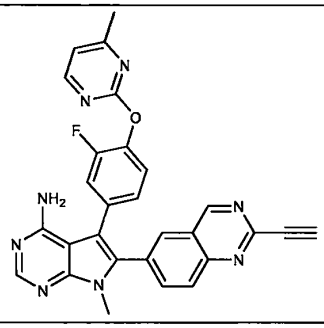
[0688]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1371		D	C
1372		D	D
1373		A	B
1374		C	B
1375		A	A

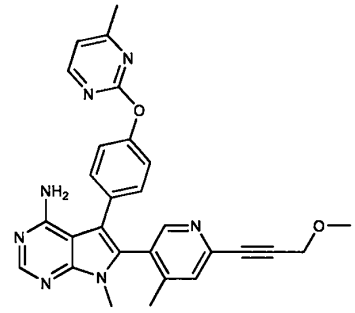
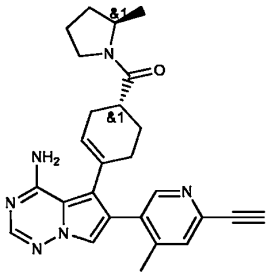
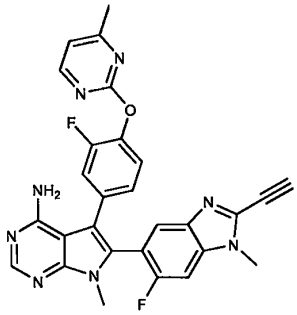
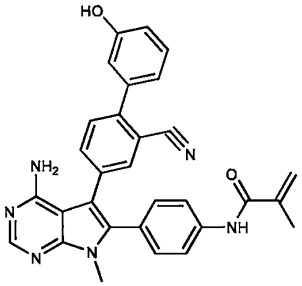
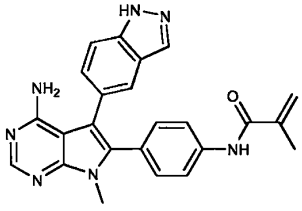
[0689]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1376		C	B
1377		C	C
1378		D	D
1379		B	A
1380		C	C

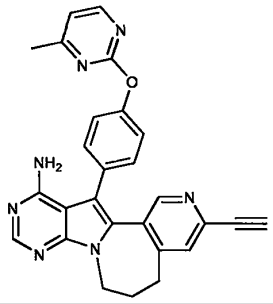
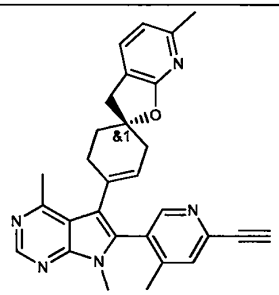
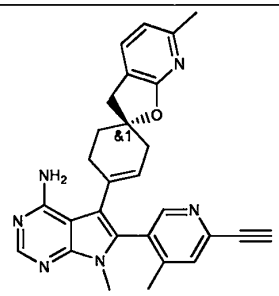
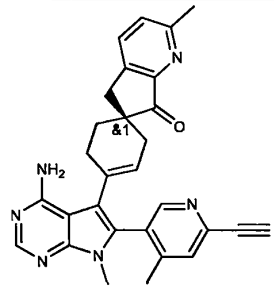
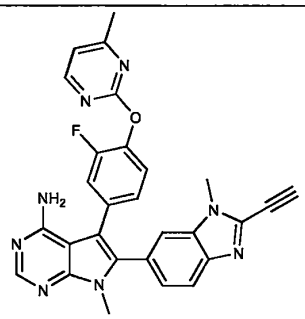
[0690]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1381		B	A
1382		A	A
1383		C	C
1384		A	B
1385		A	A

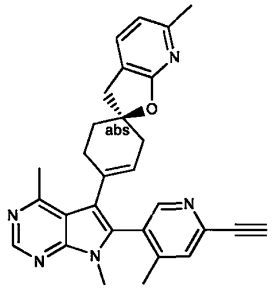
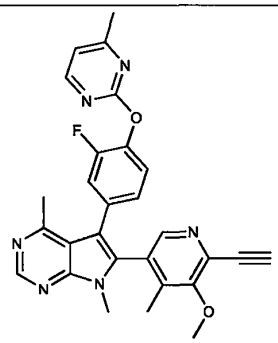
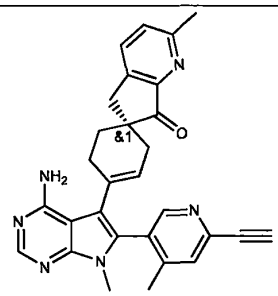
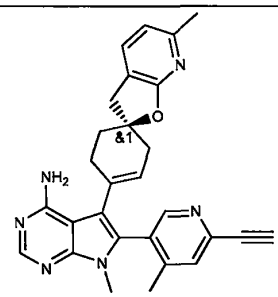
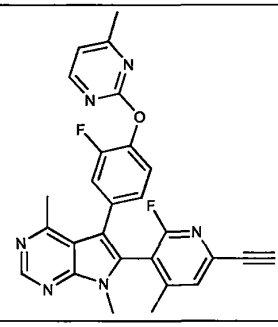
[0691]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1386		A	A
1387		D	D
1388		A	A
1389		D	C
1390		D	D

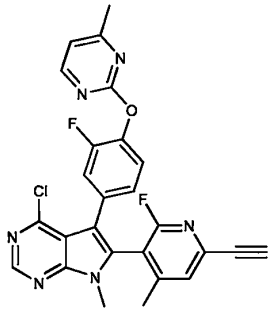
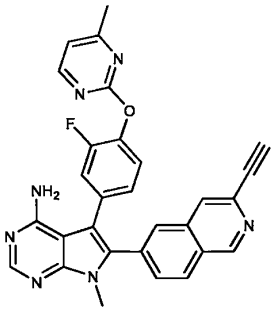
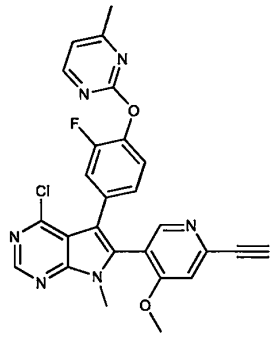
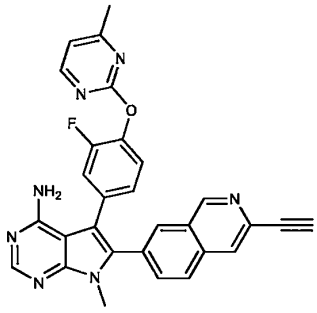
[0692]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1391		A	A
1392		D	D
1393		D	D
1394		B	B
1395		A	A

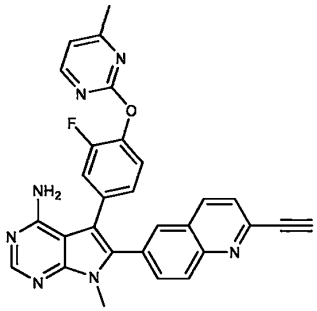
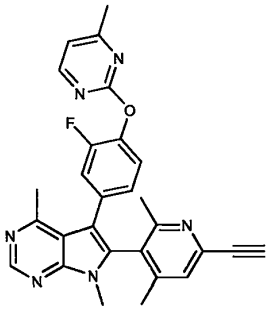
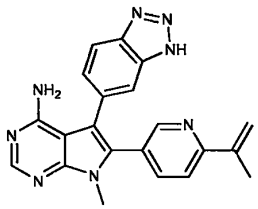
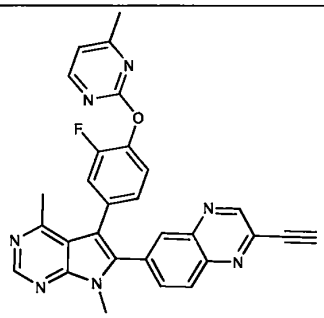
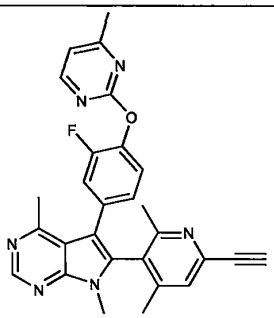
[0693]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1396		C	D
1397		C	A
1398		A	A
1399		A	B
1400		A	A

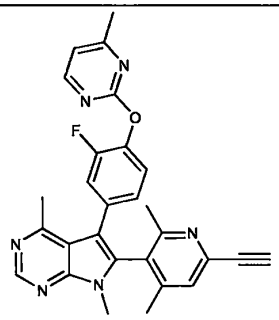
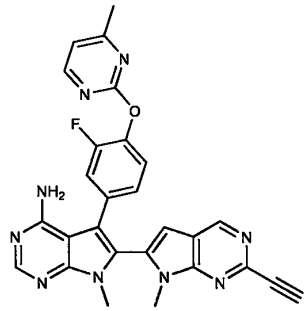
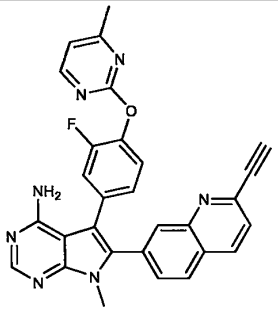
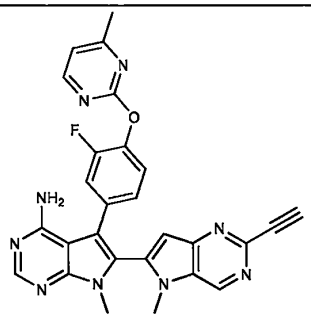
[0694]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1401		A	A
1402		D	D
1403		A	A
1404		C	C

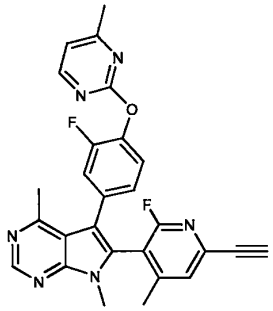
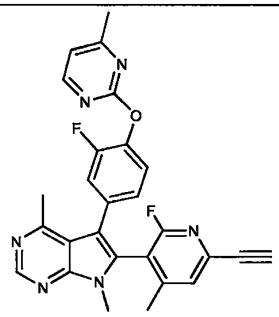
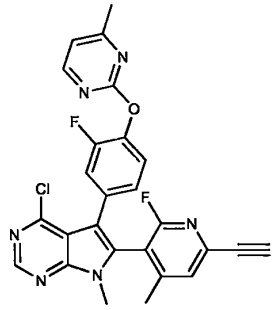
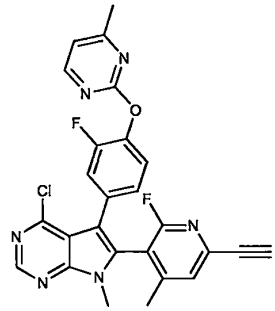
[0695]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1405		A	A
1406		A	A
1407		C	C
1408		A	B
1409		A	A

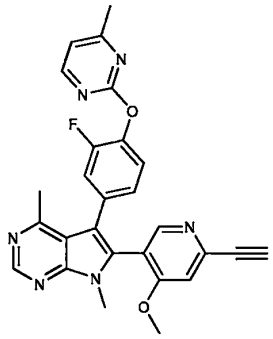
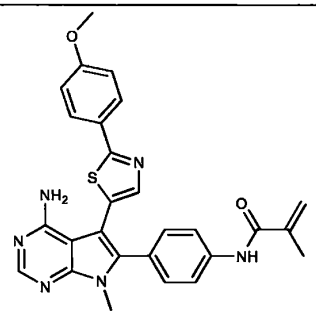
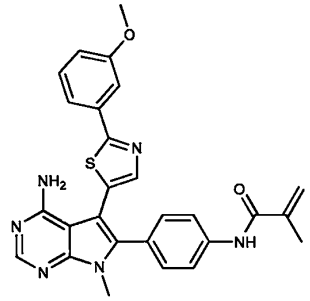
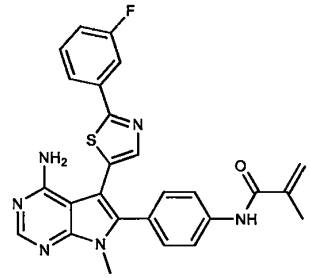
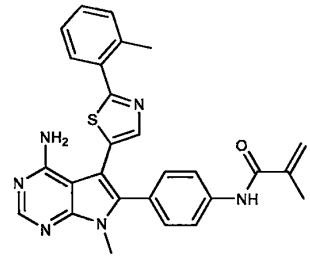
[0696]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1410		A	A
1411		A	A
1412		C	C
1413		A	A

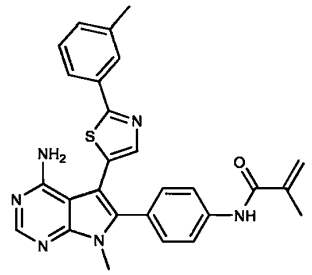
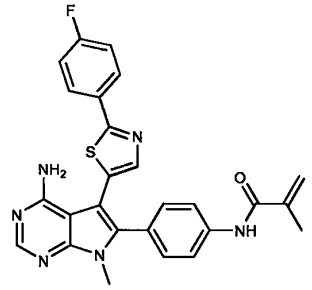
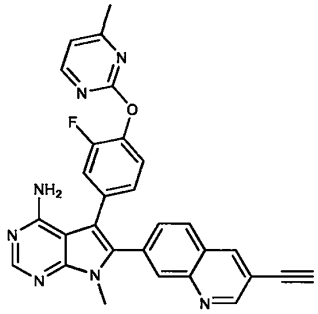
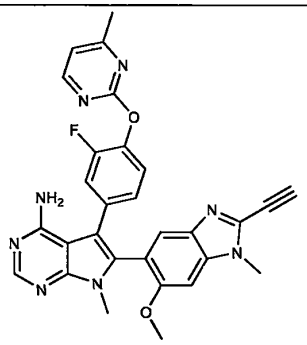
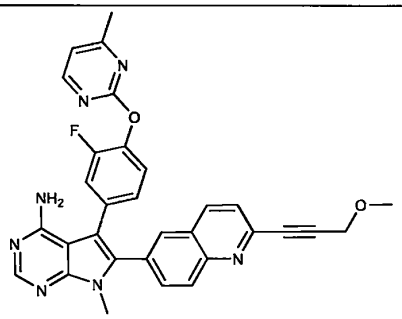
[0697]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1414	 滞转异构体 1	A	A
1415	 滞转异构体 2	A	A
1416	 滞转异构体 1	A	B
1417	 滞转异构体 2	A	A

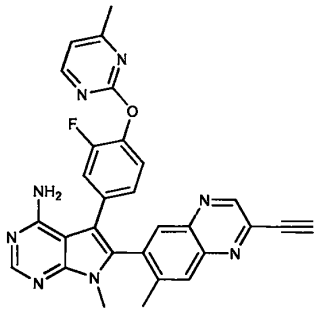
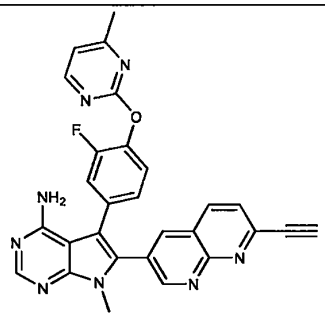
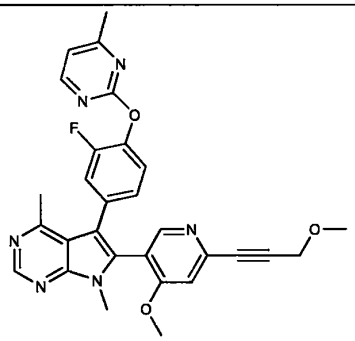
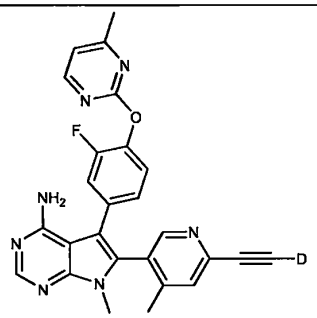
[0698]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1418		A	A
1419		A	A
1420		C	C
1421		C	C
1422		C	C

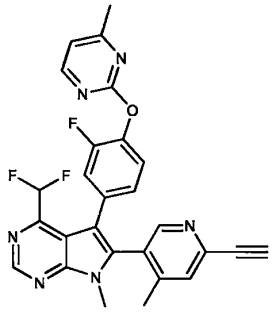
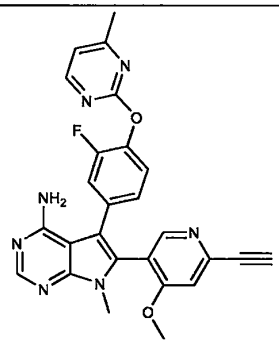
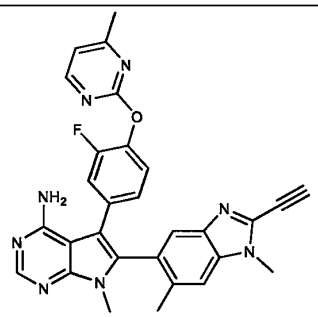
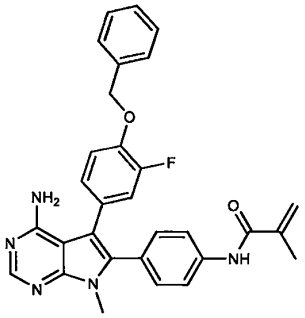
[0699]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1423		C	C
1424		B	C
1425		D	D
1426		A	A
1427		A	A

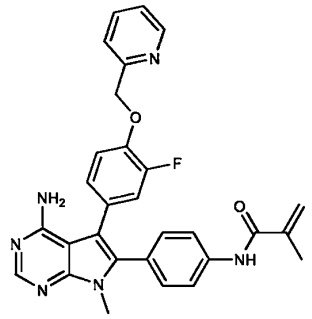
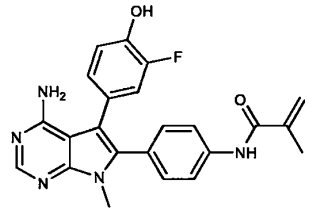
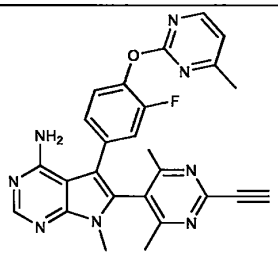
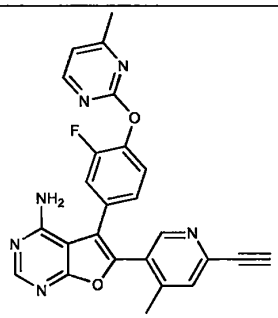
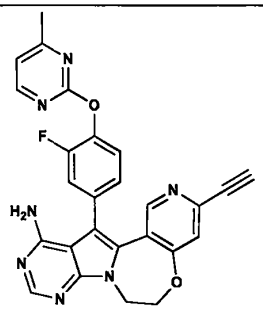
[0700]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1428		A	A
1429		A	A
1430		A	A
1431		A	A

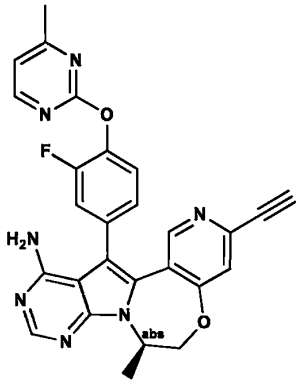
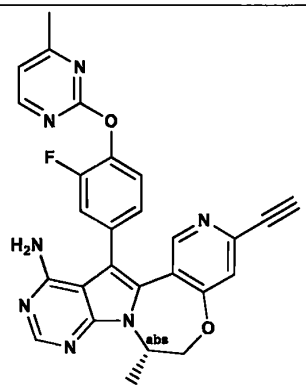
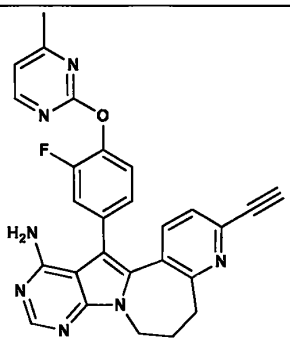
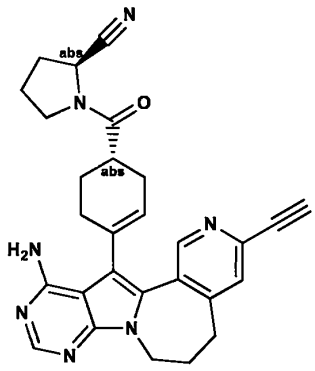
[0701]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1432		D	D
1433		A	A
1434		A	A
1435		D	D

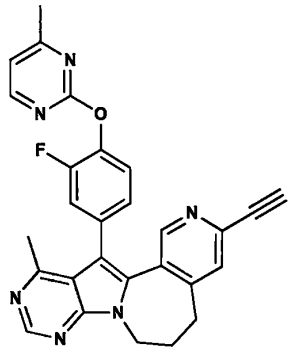
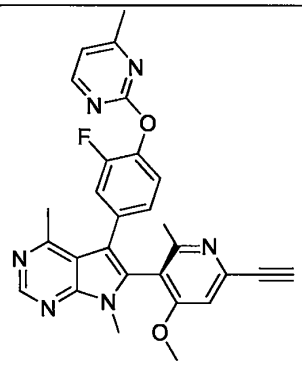
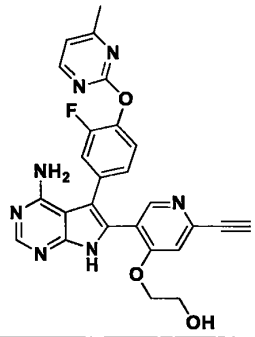
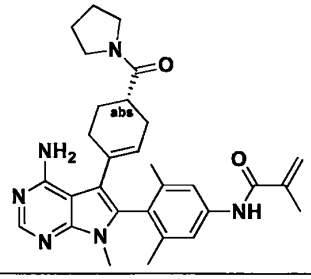
[0702]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1436		D	D
1437		C	D
1438		A	A
1439		A	A
1440		A	A

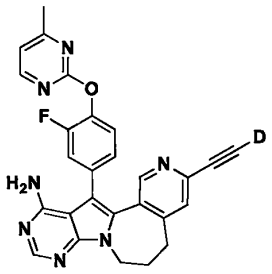
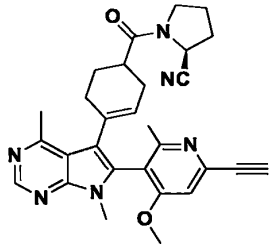
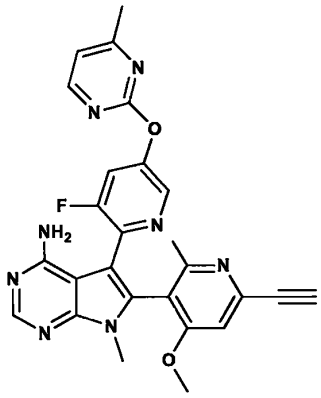
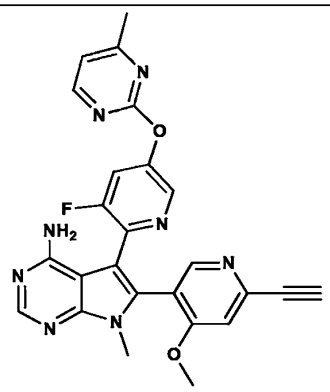
[0703]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1441		C	B
1442		D	C
1443		B	A
1444		A	

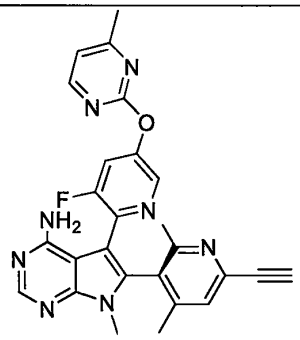
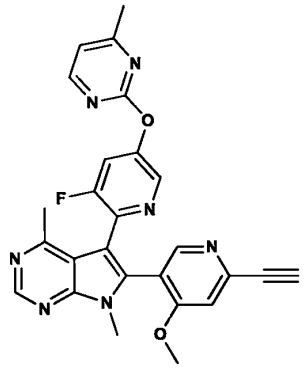
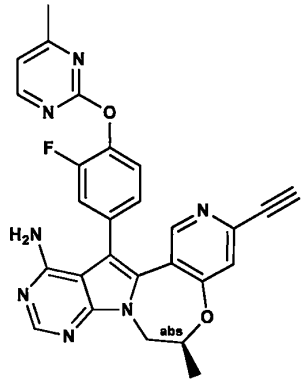
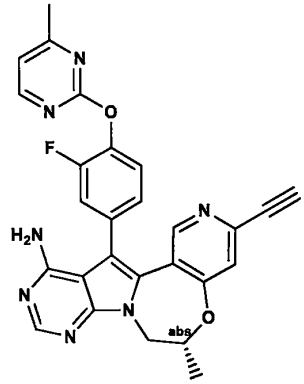
[0704]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1445		A	A
1446		A	A
1447		A	A
1448			

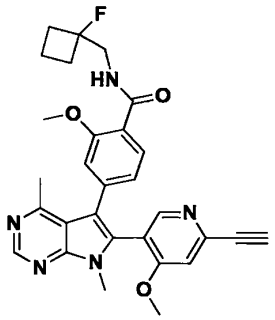
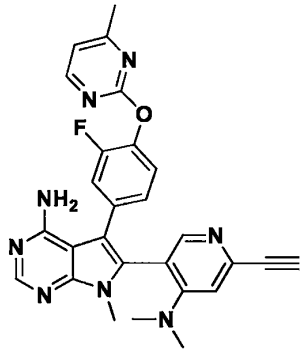
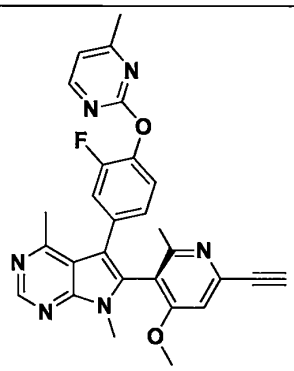
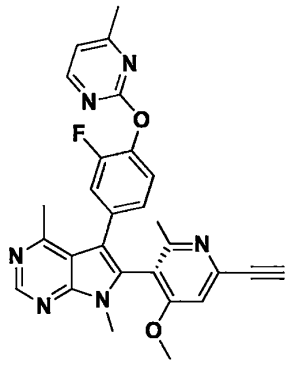
[0705]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1449		A	
1450			
1451		A	
1452		A	A

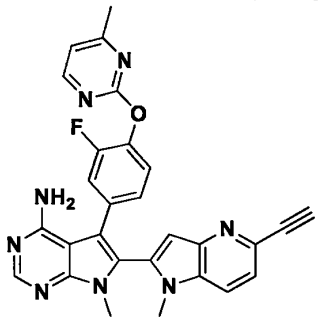
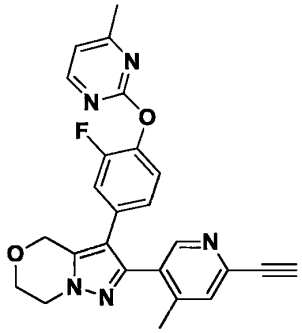
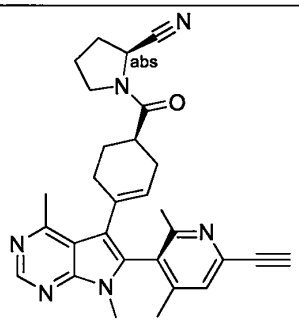
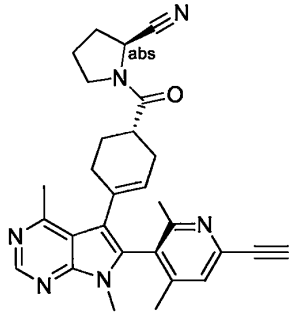
[0706]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1453		A	A
1454		A	A
1455		A	A
1456		A	A

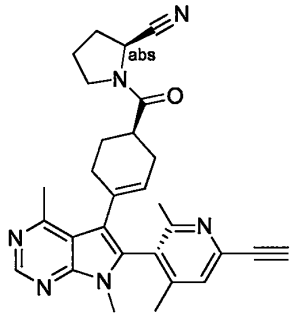
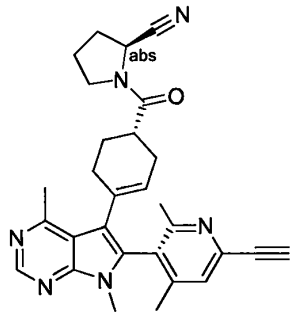
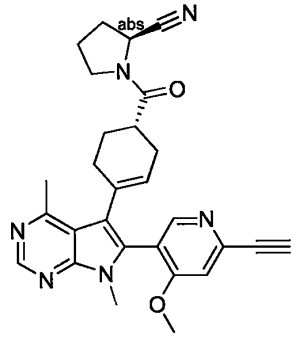
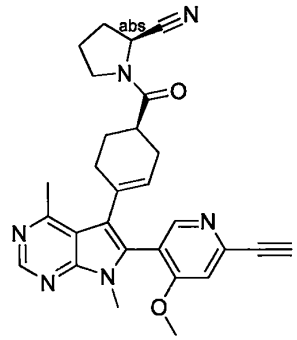
[0707]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1457		B	A
1458		A	A
1459		A	A
1460		D	C

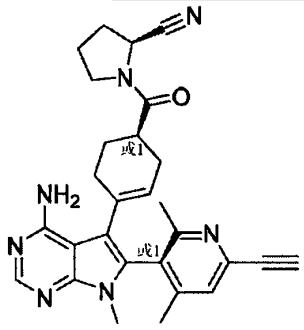
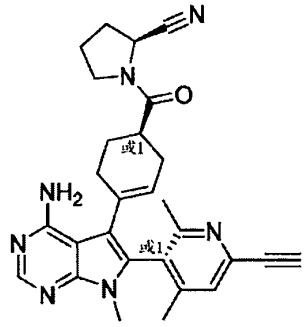
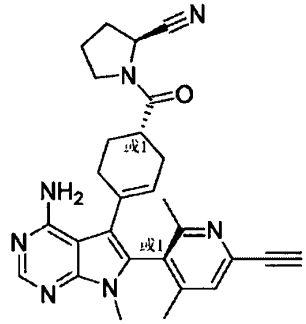
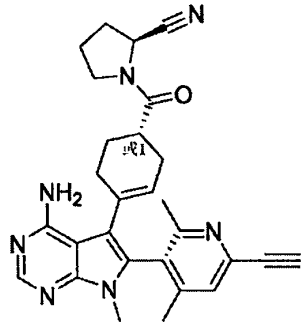
[0708]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1461		C	B
1462		D	D
1463		B	A
1464		C	C

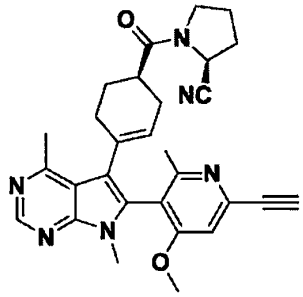
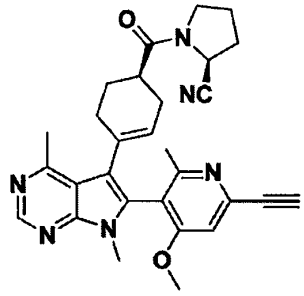
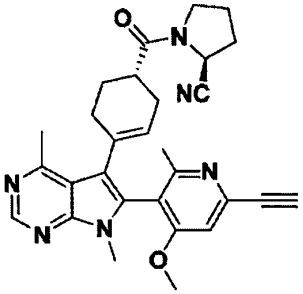
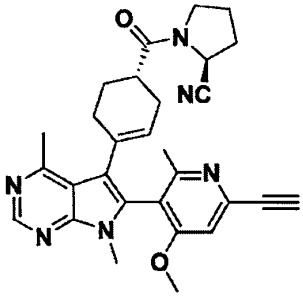
[0709]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1465		A	A
1466		B	B
1467		C	A
1468		A	A

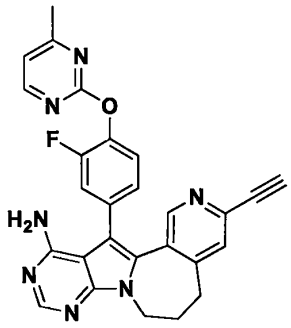
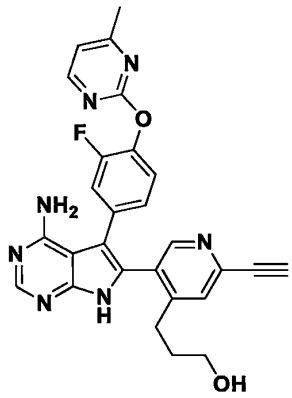
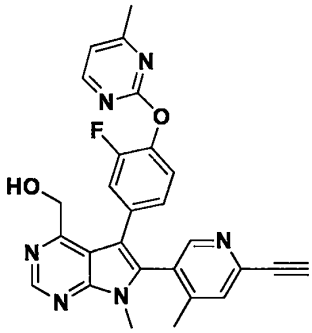
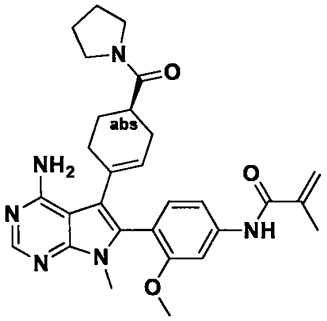
[0710]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1469		A	A
1470		A	A
1471		A	A
1472		A	A

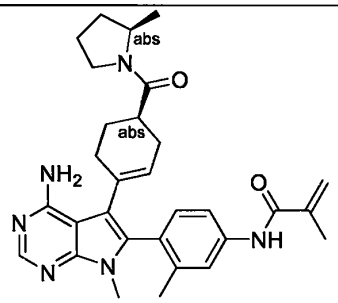
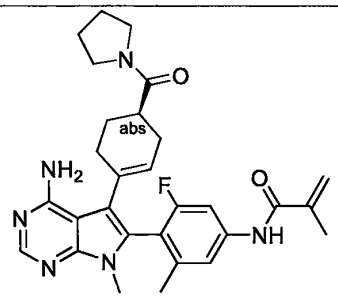
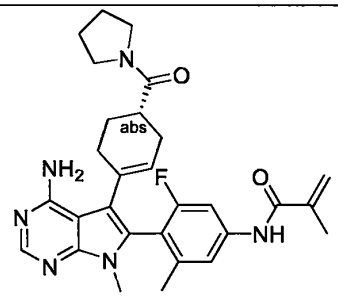
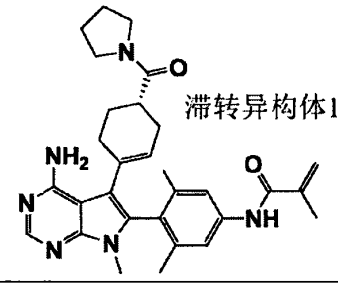
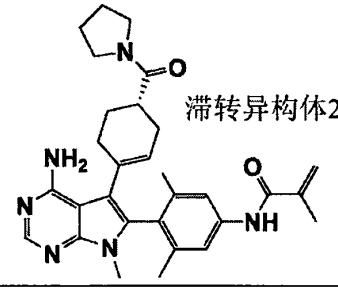
[0711]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1473	 滞转异构体1	A	A
1474	 滞转异构体2	A	A
1475	 滞转异构体1	D	D
1476	 滞转异构体2	D	C

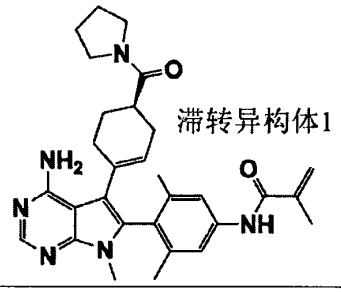
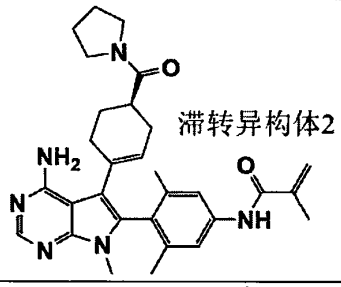
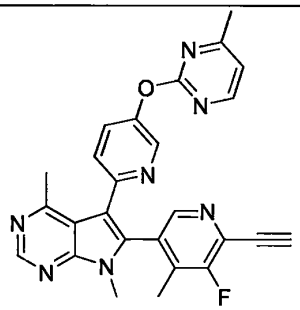
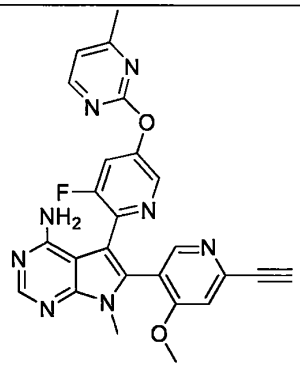
[0712]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1477		A	A
1478		C	B
1479		C	A
1480		D	C

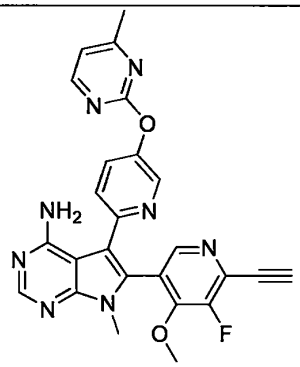
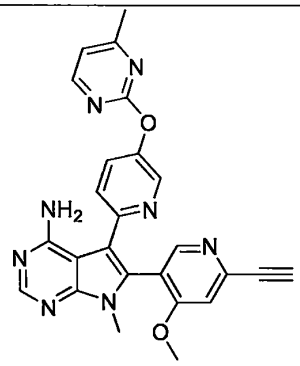
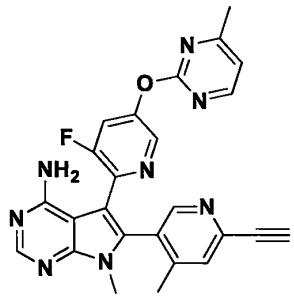
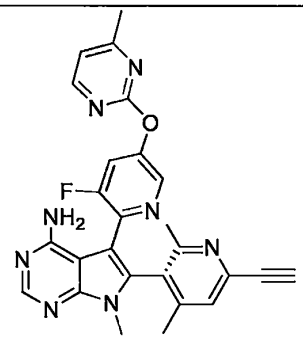
[0713]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1481		C	B
1482		A	A
1483		A	A
1484	 滞转异构体1	D	D
1485	 滞转异构体2	D	D

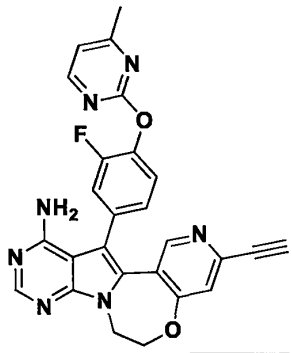
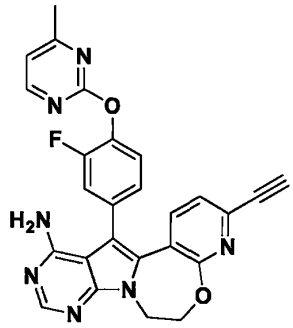
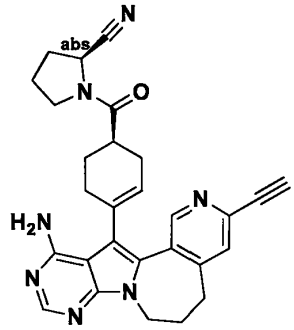
[0714]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1486	 滞转异构体1	D	D
1487	 滞转异构体2	D	D
1488		C	C
1489		A	A

[0715]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1490		D	D
1491		A	A
1492		A	A
1493		A	A

[0716]

实例	结构	生物化学 FGFR2 Caliper IC50	细胞 SNU-16 IC50
1494		A	A
1495		A	A
1496		C	

[0717] 在上表1的化学结构中,当立体异构中心用虚线或楔形键描绘且标记为“abs”(或未标记)时,化合物在所述立体中心处基本上为单一异构体(而非等摩尔混合物),且绝对立体化学如化学结构中所示。(参见例如实例146之结构)。当立体异构中心用虚线或楔形键描绘且还标记为“或1”时,化合物在所述立体异构中心处为单一异构体,但所述立体异构中心处的绝对立体化学尚未确定。(参见例如实例397及398的结构)。当立体异构中心用虚线或楔形键描绘且还标记为“与1”或“及1”时,所述化合物是所述立体异构中心处的以下两种异构体的混合物:如所绘示的结构,及其中所述立体对称中心具有相反配置的异构体。(参见例如实例581的结构)。

[0718] 上表1中所描绘的某些化合物在室温下的溶液中以跨越联芳基键的非互变滞转异构体形式存在。当联芳基键中的一个原子标记为“或1”时,此表示化合物在室温下溶液中以非互变滞转异构体形式存在,且化合物基本上为单一滞转异构体(而非等摩尔混合物)。(参见例如实例516及517的结构)。

[0719] 在一些实施例中,本发明提供上表1中的化合物,其中所述化合物所具有的生物化学FGFR2 Caliper IC_{50}是以“A”表示。在一些实施例中,本发明提供上表1中的化合物,其中所述化合物所具有的生物化学FGFR2 Caliper IC_{50}是以“A”或“B”表示。在一些实施例中,本

发明提供上表1中的化合物,其中所述化合物所具有的生物化学FGFR2 Caliper IC_{50}是以“A”或“B”或“C”表示。

[0720] 在一些实施例中,本发明提供上表1中的化合物,其中所述化合物所具有的细胞SNU-16 IC_{50}是以“A”表示。在一些实施例中,本发明提供上表1中的化合物,其中所述化合物所具有的细胞SNU-16 IC_{50}是以“A”或“B”表示。在一些实施例中,本发明提供上表1中的化合物,其中所述化合物所具有的细胞SNU-16 IC_{50}是以“A”或“B”或“C”表示。

[0721] 4.提供本发明化合物的通用方法

[0722] 本发明化合物一般可通过本领域中的技术人员已知用于类似化合物的合成和/或半合成方法及通过本文实例中详细描述的方法制备或分离。

[0723] 5.用途、配方及施药

[0724] 药学上可接受的组合物

[0725] 根据另一实施例,本发明提供一种组合物,其包含本发明化合物或其药学上可接受的衍生物及药学上可接受的载剂、佐剂或媒剂。在一些实施例中,本发明提供一种医药组合物,其包含本发明化合物及药学上可接受的载剂。本发明组合物中的化合物的量使得有效地可测量地抑制生物样品或患者中的FGFR2蛋白激酶或其突变体。在某些实施例中,本发明组合物中的化合物的量使得有效地可测量地抑制生物样品或患者中的FGFR2蛋白激酶或其突变体。在某些实施例中,本发明组合物经调配以施用于需要此类组合物的患者。在一些实施例中,本发明组合物经调配以经口施用于患者。

[0726] 如本文所用,术语“个体”及“患者”意指动物(即,动物界成员),优选哺乳动物,且最优选人类。在一些实施例中,个体是人类、小鼠、大鼠、猫、猴、犬、马或猪。在一些实施例中,个体是人类。在一些实施例中,个体是小鼠、大鼠、猫、猴、犬、马或猪。

[0727] 术语“药学上可接受的载剂、佐剂或媒剂”是指不破坏与其一起调配的化合物的药理学活性的无毒载剂、佐剂或媒剂。可用于本发明组合物中的药学上可接受的载剂、佐剂或媒剂包括(但不限于)离子交换剂、氧化铝、硬脂酸铝、卵磷脂、血清蛋白(例如人类血清白蛋白)、缓冲物质(例如磷酸盐)、甘氨酸、山梨酸、山梨酸钾、饱和植物脂肪酸的部分甘油酯混合物、水、盐或电解质(例如鱼精蛋白硫酸盐、磷酸氢二钠、磷酸氢钾、氯化钠、锌盐)、胶态二氧化硅、三硅酸镁、聚乙烯基吡咯烷酮、基于纤维素的物质、聚乙二醇、羧甲基纤维素钠、聚丙烯酸酯、蜡、聚乙烯-聚氧丙烯-嵌段聚合物、聚乙二醇及羊毛脂。

[0728] “药学上可接受的衍生物”意指本发明化合物的任何无毒的盐、酯、酯的盐或其它衍生物,其在施用于接受者时,能够直接地或间接地提供本发明化合物或其抑制活性代谢物或残余物。

[0729] 如本文所用,术语“其抑制活性代谢物或残余物”意指其代谢物或残余物也是FGFR2蛋白激酶抑制剂或其突变体。

[0730] 本发明的组合物可经口、肠胃外、通过吸入喷雾、体表、直肠、鼻、颊、阴道或经由植入式贮器施用。如本文所用,术语“肠胃外”包括皮下、静脉内、肌肉内、关节内、滑膜内、胸骨内、鞘内、肝内、病灶内及颅内注射或输注技术。组合物优选经口、腹膜内或静脉内施用。

[0731] 本发明组合物的无菌可注射形式可以是水性或油性悬浮液。这些悬浮液可根据本领域中已知的技术使用适合的分散剂或润湿剂及悬浮剂来调配。无菌可注射制剂也可以是可接受的无毒肠胃外稀释剂或溶剂中的无菌可注射溶液或悬浮液,例如1,3-丁二醇中的溶

液。在可接受的媒剂及溶剂中,可使用水、林格氏溶液(Ringer's solution)及等张氯化钠溶液。另外,常规使用无菌不挥发油作为溶剂或悬浮介质。

[0732] 出于此目的,可以使用任何温和的不挥发油,包括合成单酸或二酸甘油酯。脂肪酸(例如油酸及其甘油酯衍生物)适用于制备可注射剂,如药学上可接受的天然油,例如橄榄油或蓖麻油,尤其是其聚氧乙基化形式。这些油溶液或悬浮液也可以含有长链醇稀释剂或分散剂,例如羧甲基纤维素或常用于调配药学上可接受的剂型(包括乳化液及悬浮液)之类似分散剂。其它常用表面活性剂(例如Tween、Span及其它乳化剂)或常用于制造药学上可接受的固体、液体或其它剂型之生物可用性增强剂也可以用于调配之目的。

[0733] 本发明的药学上可接受的组合物可以可接受之任何口服剂型经口施用,包括(但不限于)胶囊、片剂、水性悬浮液或溶液。在用于口服使用之片剂之情况下,常用载剂包括乳糖及玉米淀粉。典型地亦添加润滑剂,例如硬脂酸镁。以胶囊形式经口施用时,适用的稀释剂包括乳糖及干燥玉米淀粉。当口服使用需要水性悬浮液时,将活性成分与乳化剂及悬浮剂合并。必要时,也可以添加某些甜味剂、调味剂或着色剂。

[0734] 或者,本发明的药学上可接受的组合物可以直肠施用之栓剂形式施用。这些栓剂可通过将药剂与适合的无刺激性赋形剂混合来制备,所述赋形剂在室温下为固体,但在直肠或阴道温度下为液体且因此将在直肠或阴道中熔融以释放药物。此类材料包括可可脂、蜂蜡及聚乙二醇。

[0735] 本发明的药学上可接受的组合物也可以体表施用,尤其当治疗靶标包括通过体表施用容易达到之区域或器官,包括眼睛、皮肤或低位肠道之疾病。容易制备适于这些区域或器官中的每一者的体表调配物。

[0736] 低位肠道之体表施用可以直肠栓剂调配物(参见上文)或以适合的灌肠剂调配物实现。也可以使用体表经皮贴片。

[0737] 对于体表施用而言,所提供的药学上可接受的组合物可调配为含有悬浮或溶解于一或多种载剂中的活性组分之适合软膏。用于体表施用本发明化合物的载剂包括(但不限于)矿物油、液体石蜡脂、白石蜡脂、丙二醇、聚氧乙烯、聚氧丙烯化合物、乳化蜡及水。或者,所提供的药学上可接受的组合物可以调配成适合洗剂或乳膏,其含有悬浮或溶解于一或多种药学上可接受的载剂中的活性组分。适合载剂包括(但不限于)矿物油、脱水山梨醇单硬脂酸酯、聚山梨醇酯60、鲸蜡酯蜡、鲸蜡硬脂醇、2-辛基十二醇、苯甲醇及水。

[0738] 供眼科使用时,所提供的药学上可接受的组合物可在防腐剂(例如苯扎氯铵)存在或不存在下,在pH经调节的等张无菌生理盐水中调配为微米尺寸化悬浮液,或优选在pH经调节的等张无菌生理盐水中调配为溶液。或者,供眼科使用时,药学上可接受的组合物可调配为软膏,例如石蜡脂。

[0739] 本发明的药学上可接受的组合物也可以通过鼻用气溶胶或吸入剂来施药。此类组合物是根据医药调配领域中熟知的技术制备,且可使用苯甲醇或其它适合防腐剂、增强生物可用性的吸收促进剂、氟碳化物和/或其它常规增溶剂或分散剂、在盐水中制备为溶液。

[0740] 本发明的药学上可接受的组合物优选经调配以便经口施用。此类调配物可与食物一起或不一起施用。在一些实施例中,本发明的药学上可接受的组合物不与食物一起施用。在其它实施例中,本发明的药学上可接受的组合物与食物一起施用。

[0741] 本发明化合物为了产生单一剂型的组合物而可与载剂物质合并的量将视所治疗

的患者、特定施药模式而变化。所提供的组合物优选应调配成可向接受这些组合物的患者施用剂量在每公斤体重每天0.01至100mg之间的抑制剂。

[0742] 还应了解,任何特定患者的特定剂量及治疗方案将视多种因素而定,包括所用特定化合物的活性、年龄、体重、一般健康、性别、膳食、施药时间、排出速率、药物组合,及治疗医师的判断及所治疗特定疾病的严重度。本发明化合物在组合物中的量还视组合物中的特定化合物而定。

[0743] 组合物中所用的确切剂量亦将视施药途径而定,且应根据从医者判断及各个体的情况决定。在本公开的特定实施例中,适于经口施用本发明化合物的剂量范围通常是每天约1mg至每天约1000mg。在一些实施例中,口服剂量是每天约1mg至每天约800mg。在一些实施例中,口服剂量是每天约1mg至每天约500mg。在一些实施例中,口服剂量是每天约1mg至每天约250mg。在一些实施例中,口服剂量是每天约1mg至每天约100mg。在一些实施例中,口服剂量是每天约5mg至每天约50mg。在一些实施例中,口服剂量是每天约5mg。在一些实施例中,口服剂量是约每天10mg。在一些实施例中,口服剂量是每天约20mg。在一些实施例中,口服剂量是每天约30mg。在一些实施例中,口服剂量是每天约40mg。在一些实施例中,口服剂量是每天约50mg。在一些实施例中,口服剂量是每天约60mg。在一些实施例中,口服剂量是每天约70mg。在一些实施例中,口服剂量是每天约100mg。应认识到,本文所列剂量中的任一者可构成上限或下限剂量范围,且可与任何其它剂量组合以构成包含上限及下限的剂量范围。

[0744] 在一些实施例中,药学上可接受的组合物含有所提供化合物和/或其药学上可接受的盐的浓度在以下范围内:约0.01至约90wt%、约0.01至约80wt%、约0.01至约70wt%、约0.01至约60wt%、约0.01至约50wt%、约0.01至约40wt%、约0.01至约30wt%、约0.01至约20wt%、约0.01至约2.0wt%、约0.01至约1wt%、约0.05至约0.5wt%、约1至约30wt%,或约1至约20wt%。组合物可调配为溶液、悬浮液、软膏或胶囊及其类似者。医药组合物可制备成水溶液,且可含有其它组分,例如防腐剂、缓冲剂、张力剂、抗氧化剂、稳定剂、粘度调节成分及其类似者。

[0745] 药学上可接受的载剂为本领域中的技术人元所熟知,且包括例如佐剂、稀释剂、赋形剂、填充剂、润滑剂及媒剂。在一些实施例中,载剂是稀释剂、佐剂、赋形剂或媒剂。在一些实施例中,载剂是稀释剂、佐剂或赋形剂。在一些实施例中,载剂是稀释剂或佐剂。在一些实施例中,载剂是赋形剂。

[0746] 药学上可接受的载剂的实例可包括例如水或生理盐水溶液、聚合物(例如聚乙二醇)、碳水化合物及其衍生物、油、脂肪酸或醇。作为医药载剂的油的非限制性实例包括石油、动物油、植物油或合成来源之油,例如花生油、大豆油、矿物油、芝麻油及其类似者。医药载剂也可以是生理盐水、阿拉伯胶(gum acacia)、明胶、淀粉糊、滑石、角蛋白、胶态二氧化硅、尿素及其类似者。此外,也可以使用助剂、稳定剂、增稠剂、润滑剂及着色剂。适合的医药载剂的其它实例描述于例如以下文献中:《雷明顿:药物科学和实践(Remington′s:The Science and Practice of Pharmacy)》,第22版(艾伦(Allen),诺德V.,Jr(Loyd V.,Jr)编,药学出版社(Pharmaceutical Press)(2012));《现代药学(Modern Pharmaceutics)》,第5版(亚历山大T.福罗伦斯(Alexander T.Florence),乔金·斯普曼(Juergen Siepmann),CRC出版社(2009));《药学赋形剂手册(Handbook of Pharmaceutical

Excipients)》,第7版(诺伊(Rowe),雷蒙C.(Raymond C.);舍丝基(Sheskey),鲍尔J.(Paul J.);库克(Cook),瓦尔特(Walter G.);芬顿(Fenton),马瑞E.(Marian E.)编,药学出版社(Pharmaceutical Press)(2012))(其中的每一者以全文引用的方式并入本文)。

[0747] 本文所用的药学上可接受的载剂可选自各种有机或无机物质,所述物质用作医药调配物的物质且作为镇痛剂、缓冲剂、粘合剂、崩解剂、稀释剂、乳化剂、赋形剂、增量剂、滑动剂、增溶剂、稳定剂、悬浮剂、张力剂、媒剂及粘度增加剂并入。也可以添加医药添加剂,例如抗氧化剂、芳香剂、着色剂、风味改善剂、防腐剂及甜味剂。可接受的医药载剂的实例包括羧甲基纤维素、结晶纤维素、甘油、阿拉伯胶、乳糖、硬脂酸镁、甲基纤维素、散剂、生理盐水、褐藻酸钠、蔗糖、淀粉、滑石及水以及其它。在一些实施例中,术语"药学上可接受"意指经联邦政府或州政府的管制机构批准或在美国药典或其它公认的药典中列出适用于动物且更尤其适用于人类。

[0748] 例如洗涤剂等表面活性剂也适用于调配物中。表面活性剂的特定实例包括聚乙烯吡咯烷酮、聚乙烯醇、乙酸乙烯酯及乙烯吡咯烷酮的共聚物、聚乙二醇、苯甲醇、甘露糖醇、甘油、山梨糖醇或脱水山梨糖醇的聚氧乙烯化酯;卵磷脂或羧甲基纤维素钠;或丙烯酸衍生物,例如甲基丙烯酸酯及其它;阴离子表面活性剂,例如碱性硬脂酸盐,特定地说,硬脂酸钠、硬脂酸钾或硬脂酸铵;硬脂酸钙或硬脂酸三乙醇胺;烷基硫酸盐,特定地说,月桂基硫酸钠及鲸蜡基硫酸钠;十二烷基苯磺酸钠或二辛基磺基丁二酸钠;或脂肪酸,特定地说,衍生自椰子油的那些脂肪酸;阳离子表面活性剂,例如具有式$N^+R'R''R'''R''''Y^-$的水溶性季铵盐,其中R基团相同或不同,任选地是羟基化烃基,且Y^-是强酸的阴离子,例如卤离子、硫酸根及磺酸根阴离子;溴化鲸蜡基三甲铵是可使用的阳离子表面活性剂之一,其是具有式$N^+R'R''R'''$的胺盐,其中R基团相同或不同,任选地是羟基化烃基;盐酸十八烷基胺是可使用的阳离子表面活性剂之一;非离子表面活性剂,例如任选地聚氧乙烯化的脱水山梨糖醇酯,特定地说,聚山梨醇酯80或聚氧乙烯化烷基醚;聚乙二醇硬脂酸酯、聚氧乙烯化的蓖麻油衍生物、聚甘油酯、聚氧乙烯化脂肪醇、聚氧乙烯化脂肪酸或环氧乙烷及环氧丙烷的共聚物;两性表面活性剂,例如甜菜碱的经取代的月桂基化合物。

[0749] 适合的医药载剂也可以包括赋形剂,例如淀粉、葡萄糖、乳糖、蔗糖、明胶、麦芽、稻米、面粉、白垩、硅胶、硬脂酸钠、单硬脂酸甘油酯、滑石、氯化钠、脱脂奶粉、甘油、丙烯、乙二醇、聚乙二醇300、水、乙醇、聚山梨醇酯20及其类似者。必要时,本发明组合物也可以含有少量湿润剂或乳化剂,或pH缓冲剂。

[0750] 片剂及胶囊调配物可进一步含有一或多种佐剂、粘合剂、稀释剂、崩解剂、赋形剂、填充剂或润滑剂,其各自是本领域中已知的。此类实例包括碳水化合物(例如乳糖或蔗糖)、无水磷酸氢钙、玉米淀粉、甘露糖醇、木糖醇、纤维素或其衍生物、微晶纤维素、明胶、硬脂酸盐、二氧化硅、滑石、乙醇酸淀粉钠、阿拉伯胶、调味剂、防腐剂、缓冲剂、崩解剂及着色剂。经口施用的组合物可含有一或多种任选地存在的药剂,例如甜味剂,例如果糖、阿斯巴甜糖(aspartame)或糖精;调味剂,例如胡椒薄荷、冬青油或樱桃;着色剂;及防腐剂,以提供医药学上适口的制剂。

[0751] 化合物及药学上可接受的组合物的用途

[0752] 本文所述的化合物及组合物通常适用于抑制激酶或其突变体。在一些实施例中,被本文所述化合物及组合物抑制的激酶是纤维母细胞生长因子受体(FGFR)。在一些实施例

中,被本文所述化合物及组合物抑制的激酶是FGFR1、FGFR2、FGFR3及FGFR4中的一或多者。在一些实施例中,被本文所述化合物及组合物抑制的激酶为FGFR2。

[0753] 本公开的化合物或组合物可适用于得益于FGFR2磷酸酶之抑制的应用。举例来说,本发明的FGFR2抑制剂通常适用于治疗增生性疾病。

[0754] 已在许多癌症中侦测到活化FGFR2基因融合体,包括肝内胆管癌、肝细胞癌、乳癌、前列腺癌、肺鳞状细胞癌、甲状腺癌、胃癌及卵巢癌。(I.S.巴必娜(I.S.Babina)及N.C.特勒(N.C.Turner),《自然·综述·癌症(Nat.Rev.Cancer)》2017,17:318-332;吴Y-M(Y-M Wu)等人,《癌症发现(Cancer Discov.)》3:636-647;及其中引用的参考文献)。

[0755] 已描述胃癌、乳癌、三阴性乳癌及直肠癌中存在FGFR2扩增。(I.S.巴必娜(I.S.Babina)及N.C.特勒(N.C.Turner),《自然·综述·癌症(Nat.Rev.Cancer)》2017,17:318-332;M.卡托(M.Katoh),《自然·综述·临床肿瘤学(Nat.Rev.Clin.Oncol.)》2019,16:105-122;及其中所引用的参考文献)。

[0756] 已在子宫内膜癌、非小细胞肺癌、肺鳞状细胞癌、胃癌、乳癌及尿道上皮癌中侦测到活化FGFR2突变。最常见的突变包括细胞内激酶域中的那些突变(例如N549K及K659N/M)及细胞外域中的那些突变(S252W及P253R)。FGFR2抑制剂也可以靶向经泛FGFR1-3抑制剂治疗的FGFR2中存在的抗性突变。这些突变包括V564F、E565A、N549K/H/T及L617V。(I.S.巴必娜(I.S.Babina)及N.C.特勒(N.C.Turner),《自然·综述·癌症(Nat.Rev.Cancer)》2017,17:318-332;M.卡托(M.Katoh),《自然·综述·临床肿瘤学(Nat.Rev.Clin.Oncol.)》2019,16:105-122;R.坡塔(R.Porta)等人,《肿瘤学/血液学的关键综述(Crit.Rev.Oncol.Hematol.)》2017,113:256-267;及其中引用的参考文献)。

[0757] 抑制FGFR2亦对其中FGFR2配体表达增强的肿瘤具有抗肿瘤活性(图1-4、7、8、10、21-23)(N.特勒(N.Turner)及R.格罗斯(R.Grose),《自然·综述·癌症(Nat.Rev.Cancer)》2010,10:116-129;及其中引用的参考文献)。

[0758] 抑制FGFR2亦对其中FGFR接附蛋白FRS2扩增或过度表达的肿瘤具有抗肿瘤活性。(I.S.巴必娜(I.S.Babina)及N.C.特勒(N.C.Turner),《自然·综述·癌症(Nat.Rev.Cancer)》2017,17:318-332;及其中引用的参考文献)。

[0759] FGFR2的选择性抑制通常可对其中泛FGFR1-3抑制剂有效的适应症有效。此类适应症描述于I.S.巴必娜(I.S.Babina)及N.C.特勒(N.C.Turner),《自然·综述·癌症(Nat.Rev.Cancer)》2017,17:318-332;M.卡托(M.Katoh),《自然·综述·临床肿瘤学(Nat.Rev.Clin.Oncol.)》2019,16:105-122;R.坡塔(R.Porta)等人,《肿瘤学/血液学的关键综述(Crit.Rev.Oncol.Hematol.)》2017,113:256-267;及其中引用的参考文献。

[0760] FGFR2中的活化突变亦已在颅缝早闭综合征中侦测到,包括Crouzon、Apert、Pfeiffer、Antley-Bixler、Beare-Stevenson回状颅皮、Jackson-Weiss、弯曲性骨骼发育不良,及Seathre-Chotzen样综合征,其引起颅缝的过早融合。(S.C.阿卓瑞(S.C.Azoury)等人,《国际生物科学杂志(Int.J.Biol.Sci.)》2017,13:1479-1488;及其中引用的参考文献)。FGFR2的抑制也对此类颅缝早闭综合征有效。

[0761] 本发明中所用的化合物作为FGFR激酶(例如FGFR2)或其突变体的抑制剂的活性可在活体外、活体内或细胞系中进行分析。活体外分析包括测定磷酸化活性和/或后续功能结果或活化FGFR2或其突变体的三磷酸腺苷酶活性的抑制的分析。替代的活体外分析对抑制

剂结合至FGFR2的能力进行定量。可通过在结合之前对抑制剂进行放射性标记、分离抑制剂/FGFR2复合物及测定放射性标记结合量来量测抑制剂结合。或者,可通过运作竞争实验来测定抑制剂结合,其中将新抑制剂与结合至已知放射性配体的FGFR2一起培育。适用于分析FGFR2抑制剂的代表性活体外及活体内分析包括本文所述的专利及科学出版物中所述及所揭示的那些分析。用于分析在本发明中用作FGFR2或其突变体的抑制剂的化合物的详细条件阐述于以下实例中。

[0762] 病症治疗

[0763] 所提供的化合物是FGFR2抑制剂且因此适用于治疗一或多种与FGFR2或其突变体的活性相关的病症。因此,在某些实施例中,本发明提供一种治疗个体的FGFR2介导性病症的方法,包含向有需要的个体施用治疗有效量的本发明化合物或其药学上可接受的盐,或前述任一者的药学上可接受的组合物。在某些实施例中,本发明提供一种治疗个体的FGFR2介导性病症的方法,其包含向有需要的受试者施用治疗有效量的本发明化合物或其药学上可接受的组合物。

[0764] 如本文所用,术语“FGFR2介导性”病症、疾病和/或病状意指其中已知FGFR2或其突变体起作用的任何疾病或其它有害病状。因此,本发明的另一实施例涉及治疗其中已知FGFR2或其突变体起作用的一或多种疾病或减轻其严重程度。此类FGFR2介导性病症包括(但不限于)增生性病症(例如癌症)及颅缝早闭综合征。

[0765] 在一些实施例中,本发明提供一种用于治疗一或多种病症的方法,其中所述病症是选自增生性病症及颅缝早闭综合征,所述方法包含向有需要的患者施用治疗有效量的本发明化合物或其药学上可接受的盐,或前述任一者的药学上可接受的组合物。在一些实施例中,本发明提供一种用于治疗一或多种病症的方法,其中所述病症是选自增生性病症及颅缝早闭综合征,所述方法包含向有需要的患者施用治疗有效量的本发明化合物或其药学上可接受的组合物。

[0766] 在一些实施例中,本发明提供一种治疗个体的病症的方法,所述方法包含向有需要的个体施用治疗有效量的本发明化合物或其药学上可接受的盐,或前述任一者的医药组合物,其中所述病症是胆管癌、肝癌、乳癌、前列腺癌、肺癌、甲状腺癌、胃癌、卵巢癌、直肠癌、子宫内膜癌或尿道上皮癌。在一些实施例中,病症是肝内胆管癌。在一些实施例中,所述病症是肝细胞癌。在一些实施例中,所述病症是肺鳞状细胞癌或非小细胞肺癌。

[0767] 在一些实施例中,病症是胆管癌。在一些实施例中,胆管癌是肝内胆管癌。在一些实施例中,病症是肝癌。在一些实施例中,肝癌是肝细胞癌。在一些实施例中,病症是肺癌。在一些实施例中,肺癌是肺鳞状细胞癌或非小细胞肺癌。

[0768] 在一些实施例中,本发明提供一种治疗个体的肝内胆管癌的方法,所述方法包含向有需要的个体施用治疗有效量的本发明化合物或其药学上可接受的盐,或前述任一者的医药组合物。在一些实施例中,本发明提供一种治疗个体的肝细胞癌的方法,所述方法包含向有需要的个体施用治疗有效量的本发明化合物或其药学上可接受的盐或前述任一者的医药组合物。在一些实施例中,本发明提供一种治疗个体的肺鳞状细胞癌或非小细胞肺癌的方法,所述方法包含向有需要的个体施用治疗有效量的本发明化合物或其药学上可接受的盐或前述任一者的医药组合物。

[0769] 在一些实施例中,所述病症与FGFR2信号传导相关。已知FGFR2及其它受体酪氨酸

激酶(RTK)具有多个上游及下游信号传导路径(参见特勒(Turner)及格罗斯(Grose),《自然·综述·癌症(Nat.Rev.Cancer)》(2010)10,116),并且抑制FGFR2可用于治疗与那些路径内的信号传导异常有关的病症。在一些实施例中,所述病症与FGF信号传导、JAK-STAT信号传导、PI3K-Akt信号传导、PLC-γ信号传导或MAPK信号传导相关。

[0770] 在一些实施例中,治疗方法包含以下步骤:i)鉴别需要此类治疗的个体;(ii)提供所公开的化合物或其药学上可接受的盐;及(iii)以治疗有效量施用所提供的所述化合物以治疗、遏制和/或预防需要此类治疗的个体的疾病状态或病状。

[0771] 在一些实施例中,治疗方法包含以下步骤:i)鉴别需要此类治疗的个体;(ii)提供包含所公开的化合物或其药学上可接受的盐的组合物;及(iii)以治疗有效量施用所述组合物以治疗、遏制和/或预防需要此类治疗的个体的疾病状态或病状。

[0772] 本发明的另一方面提供根据本文中的定义的化合物或其药学上可接受的盐,或前述任一者的医药组合物,其用于治疗本文所述的病症。本发明的另一方面提供根据本文中的定义的化合物或其药学上可接受的盐或前述任一者的医药组合物用于治疗本文所述病症的用途。类似地,本发明提供根据本文中的定义的化合物或其药学上可接受的盐用于制备供治疗本文所述病症的药剂的用途。

[0773] 增生性病症

[0774] 在一些实施例中,所述病症是增生性病症。在一些实施例中,增生性病症是癌症。在一些实施例中,增生性病症是白血病、乳癌、肺癌、结肠直肠癌或其组合。在一些实施例中,增生性病症是白血病。在一些实施例中,增生性病症是乳癌。在一些实施例中,增生性病症是肺癌。在一些实施例中,增生性病症是结肠直肠癌。

[0775] 在一些实施例中,增生性病症是肝内胆管癌、肝细胞癌、乳癌、前列腺癌、肺鳞状细胞癌、甲状腺癌、胃癌、卵巢癌、直肠癌、子宫内膜癌、非小细胞肺癌或尿道上皮癌。在一些实施例中,增生性病症是肝内胆管癌、肝细胞癌、乳癌、前列腺癌、肺鳞状细胞癌、甲状腺癌、胃癌或卵巢癌。在一些实施例中,增生性病症是胃癌、乳癌、三阴性乳癌或直肠癌。在一些实施例中,增生性病症是子宫内膜癌、非小细胞肺癌、肺鳞状细胞癌、胃癌、乳癌或尿道上皮癌。

[0776] 在一些实施例中,增生性病症与FGFR2中的一或多种活化突变相关。在一些实施例中,FGFR2中的活化突变是细胞内激酶域及胞外域中的一或多者的突变。在一些实施例中,FGFR2中的活化突变是细胞内激酶域之突变。在一些实施例中,FGFR2中的活化突变是胞外域的突变。在一些实施例中,FGFR2中的活化突变是选自N549K、K659N/M、S252W、P253R及其组合。在一些实施例中,FGFR2中的活化突变是N549K或K659N/M。在一些实施例中,FGFR2中的活化突变是N549K。在一些实施例中,FGFR2中的活化突变是K659N/M。在一些实施例中,FGFR2中的活化突变是S252W或P253R。在一些实施例中,FGFR2中的活化突变是S252W。在一些实施例中,FGFR2中的活化突变是P253R。

[0777] 在一些实施例中,增生性病症与FGFR2中的一或多种抗性突变相关。在一些实施例中,FGFR2中的抗性突变选自V564F、E565A、N549K/H/T及L617V及其组合。在一些实施例中,FGFR2中的抗性突变是V564F。在一些实施例中,FGFR2中的抗性突变是E565A。在一些实施例中,FGFR2中的抗性突变是N549K/H/T。在一些实施例中,FGFR2中的抗性突变是L617V。

[0778] 施药途径及剂型

[0779] 所述化合物及组合物可根据本发明的方法,使用有效治疗病症(例如增生性病症

或颅缝早闭综合征)或减轻其严重程度的任何量及任何施药途径施用。所需精确量将因个体而异,此视个体的物种、年龄及一般状况、感染严重度、特定药剂、其施用模式及其类似因素而定。本发明的化合物优选调配成容易施药及均一给药的单位剂型。如本文所用,表述"单位剂型"是指适于待治疗患者的药剂的实体不连续单元。然而应了解,本发明化合物及组合物的总日用量将由主治医师在合理医学判断范围内决定。用于任何特定患者或生物体的特定有效剂量水平将视多种因素而定,包括所治疗的病症及病症严重度;所用特定化合物的活性;所用特定组合物;患者的年龄、体重、一般健康、性别及膳食;施药时间、施药途径及所用特定化合物的排出比率;治疗持续时间;与所用特定化合物组合或同时使用的药物;及如医学技术中熟知的因素。

[0780] 本发明的药学上可接受的组合物可经口、直肠、肠胃外、脑池内、阴道内、腹膜内、体表(如通过散剂、软膏或滴剂)、经颊、作为口服或鼻用喷雾或其类似方式施用于人类及其它动物。在某些实施例中,本发明化合物可以每公斤个体体重每天约0.01mg至约50mg及优选约1mg至约25mg的剂量水平经口或肠胃外一日施用一或多次以获得所需治疗效果。

[0781] 经口施用的液体剂型包括(但不限于)药学上可接受的乳化液、微乳化液、溶液、悬浮液、糖浆及酏剂。除活性化合物以外,液体剂型可含有本领域中常用的惰性稀释剂,例如水或其它溶剂;增溶剂及乳化剂,例如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苯甲醇、苯甲酸苯甲酯、丙二醇、1,3-丁二醇、二甲基甲酰胺、油(特定地说,棉籽油、花生油、玉米油、胚芽油、橄榄油、蓖麻油及芝麻油)、甘油、四氢糠醇、聚乙二醇及脱水山梨糖醇的脂肪酸酯;及其混合物。除惰性稀释剂之外,口服组合物也可以包括佐剂,例如湿润剂、乳化剂及悬浮剂、甜味剂、调味剂及芳香剂。

[0782] 可根据已知技术、使用适合的分散剂或湿润剂及悬浮剂来调配可注射制剂,例如无菌可注射水性或油性悬浮液。无菌可注射制剂也可以是可接受的无毒性肠胃外稀释剂或溶剂中的无菌可注射溶液、悬浮液或乳化液,例如1,3-丁二醇中的溶液。在可接受的媒剂及溶剂中,可使用水、林格氏溶液、U.S.P.及等张氯化钠溶液。另外,常规使用无菌不挥发油作为溶剂或悬浮介质。出于此目的,可使用任何温和的不挥发油,包括合成的单酸甘油酯或二酸甘油酯。另外,使用脂肪酸(例如油酸)制备可注射剂。

[0783] 可注射调配物可例如通过细菌截留过滤器过滤或通过并入呈无菌固体组合物形式的灭菌剂来灭菌,所述无菌固体组合物在使用之前可溶解或分散于无菌水或其它无菌可注射介质中。

[0784] 为延长本发明化合物的作用,通常需要减缓皮下或肌肉内注射的化合物的吸收。此可通过使用水溶性不良的结晶或无定形物质的液体悬浮液来实现。化合物吸收速率则视其溶出速率而定,溶出速率又可视晶体尺寸及结晶形式而定。或者,肠胃外施用的化合物形式的延迟吸收是通过将化合物溶解或悬浮于油性媒剂中来实现。通过在例如聚丙交酯-聚乙交酯的生物可降解聚合物中形成化合物的微胶囊基质来制备可注射储槽形式。视化合物与聚合物的比率及所用特定聚合物的性质而定,可控制化合物释放速率。其它生物可降解聚合物的实例包括聚(原酸酯)及聚(酸酐)。可注射储槽式调配物也可以通过将化合物包覆于与身体组织兼容的脂质体或微乳化液中来制备。

[0785] 用于直肠或阴道施用的组合物优选栓剂,其可通过将本发明化合物与适合的非刺激性赋形剂或载剂(例如可可脂、聚乙二醇或栓剂蜡)混合来制备,所述赋形剂或载剂在环

境温度下为固体,但在体温下为液体且因此在直肠或阴道腔中熔融并释放活性化合物。

[0786] 经口施用的固体剂型包括胶囊、片剂、丸剂、散剂及颗粒剂。在此类固体剂型中,将活性化合物与至少一种药学上可接受的惰性赋形剂或载剂(例如柠檬酸钠或磷酸二钙)和/或以下混合:(a)填充剂或增量剂,例如淀粉、乳糖、蔗糖、葡萄糖、甘露糖醇及硅酸;(b)粘合剂,例如羧甲基纤维素、褐藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖及阿拉伯胶;(c)保湿剂,例如甘油;(d)崩解剂,例如琼脂--琼脂、碳酸钙、马铃薯或木薯淀粉、褐藻酸、某些硅酸盐及碳酸钠;(e)阻溶剂,例如石蜡;(f)吸收加速剂,例如季铵化合物;(g)湿润剂,例如鲸蜡醇及甘油单硬脂酸酯;(h)吸收剂,例如高岭土及膨润土;及(i)润滑剂,例如滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、月桂基硫酸钠及其混合物。在胶囊、片剂及丸剂的情况下,剂型也可以包含缓冲剂。

[0787] 在使用例如乳糖或奶糖的赋形剂以及高分子量聚乙二醇及其类似物的软填充及硬填充明胶胶囊中,也可以使用类型相似的固体组合物作为填充剂。片剂、糖衣药丸、胶囊、丸剂及颗粒剂的固体剂型可制备有包衣及外壳,例如肠溶包衣及医药调配技术中熟知的其它包衣。其可任选地含有乳浊剂,且也可以具有仅在或优先在肠道的某一部分中释放或任选地以延迟方式释放活性成分的组成。可使用的包埋组合物的实例包括聚合物质及蜡。在使用例如乳糖或奶糖的赋形剂以及高分子量聚乙二醇及其类似物的软填充及硬填充明胶胶囊中,可以使用类型相似的固体组合物作为填充剂。

[0788] 活性成分可与一或多种如上文所指出的赋形剂一起呈微囊封形式。片剂、糖衣药丸、胶囊、丸剂及颗粒剂的固体剂型可制备有包衣及外壳,例如肠溶包衣、释放控制包衣及医药调配技术中熟知的其它包衣。在此类固体剂型中,可将活性化合物与至少一种惰性稀释剂(例如蔗糖、乳糖或淀粉)混合。如同一般实务,此类剂型也可以包含除惰性稀释剂以外的其它物质,例如制片润滑剂及其它制片助剂,例如硬脂酸镁及微晶纤维素。在胶囊、片剂及丸剂的情况下,剂型可以包含缓冲剂。其可任选地含有乳浊剂,且也可以具有仅在或优先在肠道的某一部分中释放或任选地以延迟方式释放活性成分的组成。可使用的包埋组合物的实例包括聚合物质及蜡。

[0789] 体表或经皮施用本发明化合物的剂型包括软膏、糊剂、乳膏、洗剂、凝胶、散剂、溶液、喷雾剂、吸入剂或贴片。可在必要时,将活性组分在无菌条件下与药学上可接受的载剂及任何必需防腐剂或缓冲剂混合。眼用调配物、滴耳剂和滴眼剂也涵盖于本发明的范畴内。另外,本发明涵盖使用经皮贴片,其具有向身体提供化合物的可控递送的额外优势。此类剂型可通过将化合物溶解或分配于适当介质中来制备。也可以使用吸收增强剂来增强化合物穿越皮肤的流动。可通过提供速率控制膜或使化合物分散于聚合物基质或凝胶中来控制速率。

[0790] 给药的量及疗法

[0791] 根据本公开的方法,向个体施用治疗有效量的本公开的化合物,例如以减少或改善个体的病症的症状。此量容易通过本领域中的技术人元基于已知程序判定,所述程序包括活体内确立的滴定曲线的分析以及本文所揭示的方法及分析。

[0792] 在一些实施例中,方法包含施用治疗有效剂量的本公开的化合物。在一些实施例中,治疗有效剂量为每公斤体重至少约0.0001mg、每公斤体重至少约0.001mg、每公斤体重至少约0.01mg、每公斤体重至少约0.05mg、每公斤体重至少约0.1mg、每公斤体重至少约

0.25mg、每公斤体重至少约0.3mg、每公斤体重至少约0.5mg、每公斤体重至少约0.75mg、每公斤体重至少约1mg、每公斤体重至少约2mg、每公斤体重至少约3mg、每公斤体重至少约4mg、每公斤体重至少约5mg、每公斤体重至少约6mg、每公斤体重至少约7mg、每公斤体重至少约8mg、每公斤体重至少约9mg、每公斤体重至少约10mg、每公斤体重至少约15mg、每公斤体重至少约20mg、每公斤体重至少约25mg、每公斤体重至少约30mg、每公斤体重至少约40mg、每公斤体重至少约50mg、每公斤体重至少约75mg、每公斤体重至少约100mg、每公斤体重至少约200mg、每公斤体重至少约250mg、每公斤体重至少约300mg、每公斤体重至少约350mg、每公斤体重至少约400mg、每公斤体重至少约450mg、每公斤体重至少约500mg、每公斤体重至少约550mg、每公斤体重至少约600mg、每公斤体重至少约650mg、每公斤体重至少约700mg、每公斤体重至少约750mg、每公斤体重至少约800mg、每公斤体重至少约900mg，或每公斤体重至少约1000mg。应认识到，本文所列剂量中的任一者可构成上限或下限剂量范围，且可与任何其它剂量组合以构成包含上限及下限的剂量范围。

[0793] 在一些实施例中，治疗有效剂量的范围为每公斤体重约0.1mg至约10mg、每公斤体重约0.1mg至约6mg、每公斤体重约0.1mg至约4mg或每公斤体重约0.1mg至约2mg。

[0794] 在一些实施例中，治疗有效剂量的范围为约1至500mg、约2至150mg、约2至120mg、约2至80mg、约2至40mg、约5至150mg、约5至120mg、约5至80mg、约10至150mg、约10至120mg、约10至80mg、约10至40mg、约20至150mg、约20至120mg、约20至80mg、约20至40mg、约40至150mg、约40至120mg或约40至80mg。

[0795] 在一些实施例中，方法包含单次给药或施药(例如单次注射或沉积)。或者，在一些实施例中，方法包含每日一次、每日两次、每日三次或每日四次施用于有需要的个体，历时约2至约28天，或约7至约10天，或约7至约15天，或更久。在一些实施例中，方法包含长期施药。在又其它实施例中，方法包含在数周、数月、数年或数十年期间内施药。在另其它实施例中，方法包含在数周期间内施药。在另其它实施例中，方法包含在数月期间内施药。在另其它实施例中，方法包含在数年期间内施药。在又其它实施例中，方法包含在数十年期间内施药。

[0796] 施药剂量可视已知因素而变化，例如活性成分的药效学特征以及其施药模式及途径；活性成分的施用时间；接受者的年龄、性别、健康状况及体重；症状的性质及程度；并行治疗的种类、治疗频率及所需效果；以及排出速率。这些因素皆容易确定且本领域中的技术人元可利用这些因素来调整或滴定剂量和/或给药方案。

[0797] 蛋白激酶的抑制

[0798] 根据一个实施例，本发明涉及抑制生物样品中的蛋白激酶活性的方法，其包含使所述生物样品与本发明化合物或包含所述化合物的组合物接触的步骤。

[0799] 根据另一个实施例，本发明涉及一种抑制生物样品中的FGFR2或其突变体的活性的方法，其包含使所述生物样品与本发明化合物或包含所述化合物的组合物接触的步骤。在某些实施例中，本发明涉及一种可逆地抑制生物样品中的FGFR2或其突变体的活性的方法，其包含使所述生物样品与本发明化合物或包含所述化合物的组合物接触的步骤。在某些实施例中，本发明涉及不可逆地抑制生物样品中的FGFR2或其突变体的活性的方法，其包含使所述生物样品与本发明化合物或包含所述化合物的组合物接触的步骤。

[0800] 在一些实施例中，本发明涉及不可逆地抑制FGFR2或其突变体的方法，其中本发明

化合物与FGFR2或其突变体形成共价键。在一些实施例中,本发明涉及不可逆地抑制FGFR2或其突变体的方法,其中本发明化合物在所述化合物的R^W与FGFR2或其突变体的半胱氨酸之间形成共价键。在一些实施例中,本发明涉及不可逆地抑制FGFR2或其突变体的方法,其中本发明化合物在所述化合物的R^W与FGFR2或其突变体的Cys491之间形成共价键。

[0801] 根据另一实施例,本发明涉及被本发明化合物不可逆地抑制的FGFR2或其突变体。在一些实施例中,本发明涉及共价键结至本发明化合物的FGFR2或其突变体。在一些实施例中,本发明涉及共价键结至本发明化合物的FGFR2或其突变体,其中共价键介于所述化合物的R^W与FGFR2或其突变体的半胱氨酸之间。在一些实施例中,本发明涉及共价键结至本发明化合物的FGFR2或其突变体,其中共价键介于所述化合物的R^W与FGFR2或其突变体的Cys491之间。

[0802] 在另一实施例中,本发明提供相对于FGFR1、FGFR3及FGFR4中的一或多者选择性地抑制FGFR2的方法。在一些实施例中,本发明化合物相对于FGFR1、FGFR3及FGFR4具有超过5倍的选择性。在一些实施例中,本发明化合物相对于FGFR1、FGFR3及FGFR4具有超过10倍的选择性。在一些实施例中,本发明化合物相对于FGFR1、FGFR3及FGFR4具有超过50倍的选择性。在一些实施例中,本发明化合物相对于FGFR1、FGFR3及FGFR4具有超过100倍的选择性。在一些实施例中,本发明化合物相对于FGFR1、FGFR3及FGFR4具有超过200倍的选择性。

[0803] 如本文所用,术语“生物样品”包括(不限于)细胞培养物或其提取物;获自哺乳动物之切片材料或其提取物;及血液、唾液、尿液、粪便、精液、泪液或其它体液或其提取物。

[0804] 抑制生物样品中的FGFR2(或其突变体)活性适用于本领域中的技术人元已知的多种目的。此类目的的实例包括(但不限于)输血、器官移植、生物样本储存及生物分析。

[0805] 本发明的另一实施例涉及一种抑制患者中的蛋白激酶活性的方法,其包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤。

[0806] 根据另一个实施例,本发明涉及一种抑制患者中的FGFR2或其突变体的活性的方法,其包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤。根据某些实施例,本发明涉及一种可逆地或不可逆地抑制患者中的FGFR2或其突变体中的一或多者的活性的方法,包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤。根据另一个实施例,本发明涉及一种可逆地抑制患者中的FGFR2或其突变体中的一或多者的活性的方法,其包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤。根据某些实施例,本发明涉及一种不可逆地抑制患者中的FGFR2或其突变体中的一或多者的活性的方法,包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤。

[0807] 在一些实施例中,本发明涉及一种不可逆地抑制患者中的FGFR2或其突变体中的一或多者的活性的方法,包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤,其中所述化合物与FGFR2或其突变体形成共价键。在一些实施例中,本发明涉及一种不可逆地抑制患者中的FGFR2或其突变体中的一或多者的活性的方法,包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤,其中所述化合物在所述化合物的R^W与FGFR2或其突变体的半胱氨酸之间形成共价键。在一些实施例中,本发明涉及一种不可逆地抑制患者中的FGFR2或其突变体中的一或多者的活性的方法,包含向所述患者施用本发明化合物或包含所述化合物的组合物的步骤,其中所述化合物在所述化合物的R^W与FGFR2或其突变体的Cys491之间形成共价键。

[0808] 根据另一个实施例,本发明提供一种治疗有需要的患者的由FGFR2或其突变体介导的病症的方法,包含向所述患者施用根据本发明的化合物或其药学上可接受的组合物的步骤。此类病症详细描述于本文中。在一些实施例中,本发明提供一种用于治疗有需要的患者的由FGFR2或其突变体介导的病症的方法,包含向所述患者施用本发明化合物或其药学上可接受的组合物的步骤,其中所述化合物可逆地抑制FGFR2或其突变体。

[0809] 在一些实施例中,本发明提供一种治疗有需要的患者的由FGFR2或其突变体介导的病症的方法,包含向所述患者施用本发明化合物或其药学上可接受的组合物的步骤,其中所述化合物不可逆地抑制FGFR2或其突变体。在一些实施例中,本发明提供一种用于治疗有需要的患者的由FGFR2或其突变体介导的病症的方法,包含向所述患者施用本发明化合物或其药学上可接受的组合物的步骤,其中所述化合物与FGFR2或其突变体形成共价键。在一些实施例中,本发明提供一种治疗有需要的患者的由FGFR2或其突变体介导的病症的方法,包含向所述患者施用本发明化合物或其药学上可接受的组合物的步骤,其中所述化合物在所述化合物的R^{W}与FGFR2或其突变体的半胱氨酸之间形成共价键。在一些实施例中,本发明提供一种用于治疗有需要的患者的由FGFR2或其突变体介导的病症的方法,包含向所述患者施用本发明化合物或其药学上可接受的组合物的步骤,其中所述化合物在所述化合物的R^{W}与FGFR2或其突变体的Cys491之间形成共价键。

[0810] 根据另一个实施例,本发明提供一种抑制个体中的FGFR2或其突变体的信号传导活性的方法,包含向有需要的个体施用治疗有效量的本发明化合物或其药学上可接受的组合物。在一些实施例中,本发明提供一种抑制个体中的FGFR2信号传导活性的方法,所述方法包含向有需要的个体施用治疗有效量的本发明化合物或其药学上可接受的组合物。

[0811] 在一些实施例中,本发明提供一种用于治疗有需要的患者的由FGFR2或其突变体介导的病症的方法,包含向所述患者施用本发明化合物或其药学上可接受的组合物的步骤,其中所述化合物可逆地抑制FGFR2或其突变体。

[0812] 本文所述的化合物也可以经由并入催化FGFR2毁坏的药剂中来抑制FGFR2功能。举例来说,可将化合物并入靶向蛋白水解的嵌合体(PROTAC)中。PROTAC是双官能分子,其中一个部分能够接合E3泛蛋白连接酶且另一部分能够结合希望通过细胞蛋白质量控制机制进行降解的靶蛋白。靶蛋白募集至特定E3连接酶以便将其标记用于毁坏(即,泛素化)且随后通过蛋白酶体降解。可使用任何E3连接酶。PROTAC中的与E3接合酶接合的部分经由连接基团连接至PROTAC中的与靶蛋白接合的部分,所述连接基团由可变原子链组成。FGFR2募集至E3连接酶将因此毁坏FGFR2蛋白。可变原子链可包括例如环、杂原子和/或重复聚合物单元。其可为刚性或柔性的。其可使用有机合成技术中的标准技术连接至上述两个部分。

[0813] 组合疗法

[0814] 视待治疗的特定病症、病状或疾病而定,可将通常为了治疗所述病状而施用的其它治疗剂与本发明的化合物及组合物组合施用。如本文所用,通常为了治疗特定疾病或病状而施用的其它治疗剂被称为“适于所治疗的疾病或病状”。

[0815] 因此,在某些实施例中,治疗方法包含将本发明的化合物或组合物与一或多种其它治疗剂组合施用。在某些其它实施例中,治疗方法包含将本发明的化合物或组合物作为单独的治疗剂施用。

[0816] 在一些实施例中,一或多种其它治疗剂是选自抗体、抗体-药物结合物、激酶抑制

剂、免疫调节剂及组蛋白去乙酰酶抑制剂。在一些实施例中,一或多种其它治疗剂是选自以下药剂或其药学上可接受的盐:BCR-ABL抑制剂:例如伊马替尼(imatinib)、伊罗替尼(inilotinib)、尼罗替尼(nilotinib)、达沙替尼(dasatinib)、伯舒替尼(bosutinib)、普纳替尼(ponatinib)、巴氟替尼(bafetinib)、达鲁舍替(danusertib)、塞卡替尼(saracatinib)、PF03814735;ALK抑制剂(参见达德(Dardaei)等人,2018,《自然·医药(Nat Med.)》;24(4):512-517):例如克卓替尼(crizotinib)、NVP-TAE684、色瑞替尼(ceritinib)、艾乐替尼(alectinib)、布加替尼(brigatinib)、恩曲昔尼(entrecinib)、罗拉替尼(lorlatinib);BRAF抑制剂(参见普拉豪拉(Prahallad)等人,2015,《细胞报道(Cell Rep.)》12,1978-1985):例如维罗非尼(vemurafenib)、达拉非尼(dabrafenib);FGFR抑制剂:例如英非替尼(infigratinib)、多韦替尼(dovitinib)、厄达替尼(erdafitinib)、BLU-554、AZD4547;FLT3抑制剂:例如舒尼替尼(sunitinib)、米哚妥林(midostaurin)、丹鲁替尼(tanutinib)、索拉非尼(sorafenib)、来他替尼(lestaurtinib)、喹杂替尼(quizartinib)及克诺拉尼(crenolanib);MEK抑制剂(参见非德勒(Fedele)等人,2018,BioRxiv 307876;妥瑞-阿索(Torres-Ayuso)等人,2018,《癌症发现(Cancer Discov.)》8,1210-1212;及翁(Wong)等人,2016,《肿瘤靶标(Oncotarget.)》2016年10月4日;7(40):65676-65695):例如曲美替尼(trametinib)、考比替尼(cobimetinib)、毕尼替尼(binimetinib)、司美替尼(selumetinib);ERK抑制剂,例如优立替尼(ulixertinib)、MK-8353、LY-3214996;VEGF受体抑制剂,例如贝伐单抗(bevacizumab)、阿西替尼(axitinib)、阿柏西普(aflibercept)、布立尼布(brivanib)、莫替沙尼(motesanib)、帕瑞肽(pasireotide)、索拉非尼(sorafenib);酪氨酸激酶抑制剂,例如埃罗替尼(erlotinib)、立尼法尼(linifanib)、舒尼替尼(sunitinib)、帕佐泮尼(pazopanib);表皮生长因子受体(EGFR)抑制剂:吉非替尼(gefitnib)、奥希替尼(osimertinib)、西妥昔单抗(cetuximab)、帕尼单抗(panitumumab);HER2受体抑制剂,例如曲妥珠单抗(trastuzumab)、来那替尼(neratinib)、拉帕替尼(lapatinib)、拉帕替尼;MET抑制剂:例如克卓替尼(crizotinib)、卡博替尼(cabozantinib);CD20抗体:例如利妥昔单抗(rituximab)、托西莫单抗(tositumomab)、奥伐木单抗(ofatumumab);DNA合成抑制剂:例如卡培他滨(capecitabine)、吉西他滨(gemcitabine)、奈拉滨(nelarabine)、羟基脲(hydroxycarbamide);抗赘生性药剂:例如奥沙利铂(oxaliplatin)、顺铂(cisplatin);HER二聚合抑制剂:例如帕妥珠单抗(pertuzumab);人类颗粒球群落刺激因子(G-CSF)调节剂:例如非格司亭(filgrastim);免疫调节剂:例如阿托珠单抗(afutuzumab)、来那度胺(lenalidomide)、沙立度胺(thalidomide)、泊利度胺(pomalidomide);CD40抑制剂:例如达西珠单抗(dacetuzumab);促细胞凋亡受体促效剂(PARA):例如杜拉乐明(dulanermin);热休克蛋白(HSP)抑制剂:例如坦螺旋霉素(tanespimycin)(17-烯丙基氨基-17-去甲氧基格尔德霉素(desmethoxygeldanamycin));Hedgehog拮抗剂:例如维莫德吉(vismodegib);蛋白酶体抑制剂:硼替佐米(bortezomib);PI3K抑制剂:例如皮克昔布(pictilisib)、达妥昔布(dactolisib)、布帕昔布(buparlisib)、泰尼西布(taselisib)、艾德昔布(idelalisib)、杜维昔布(duvelisib)、温布昔布(umbralisib);磷脂酶A2抑制剂:例如阿那格雷(anagrelide);BCL-2抑制剂:例如维纳妥拉(venetoclax);芳香酶抑制剂:依西美坦(exemestane)、来曲唑(letrozole)、阿那曲唑(anastrozole)、法洛德克斯(faslodex)、他

莫昔芬(tamoxifen);拓朴异构酶I抑制剂:例如伊立替康(irinotecan)、拓朴替康(topotecan);拓朴异构酶II抑制剂:例如依托泊苷(etoposide)、替尼泊苷(teniposide);mTOR抑制剂:例如坦罗莫司(temsirolimus)、地磷莫司(ridaforolimus)、依维莫司(everolimus)、西罗莫司(sirolimus);破骨骨骼再吸收抑制剂:例如唑来膦酸(zoledronic acid);CD33抗体药物结合物:例如吉妥珠单抗奥佐米星(gemtuzumab ozogamicin);CD22抗体药物结合物:例如英妥珠单抗奥佐米星(inotuzumab ozogamicin);CD20抗体药物结合物:例如替伊莫单抗(ibritumomab tiuxetan);生长抑素类似物:例如奥曲肽(octreotide);白介素-11(IL-11):例如奥普瑞白介素(oprelvekin);合成红血球生成素:例如阿法达贝泊汀(darbepoetin alfa);核因子κB的受体活化因子(RANK)抑制剂:例如地诺单抗(denosumab);血小板生成素模拟肽:例如罗米司亭(romiplostim);细胞生长刺激剂:例如帕利夫明(palifermin);抗胰岛素样生长因子-1受体(IGF-1R)抗体:例如非吉单抗(figitumumab);抗CS1抗体:例如埃罗妥珠单抗(elotuzumab);CD52抗体:例如阿仑单抗(alemtuzumab);CTLA-4抑制剂:例如曲美单抗(tremelimumab)、伊匹单抗(ipilimumab);PD1抑制剂:例如尼沃单抗(nivolumab)、派立珠单抗(pembrolizumab);免疫粘附素:例如皮立珠单抗(pidilizumab)、AMP-224;PDL1抑制剂:例如MSB0010718C、YW243.55.S70、MPDL3280A、MEDI-4736、MSB 0010718C或MDX-1105;LAG-3抑制剂:例如BMS-986016;GITR促效剂;GITR融合蛋白及抗GITR抗体;组蛋白去乙酰酶抑制剂(HDI):例如伏立诺他(voninostat);抗CTLA4抗体:例如曲美单抗(tremelimumab)、伊匹单抗(ipilimumab);烷基化剂:例如替莫唑胺(temozolomide)、放线菌素d(dactinomycin)、美法仑(melphalan)、六甲蜜胺卡莫司汀(altretamine carmustine)、苯达莫司汀(bendamustine)、白消安(busulfan)、卡铂(carboplatin)、洛莫司汀(lomustine)、顺铂(cisplatin)、苯丁酸氮芥(chlorambucil)、环磷酰胺(cyclophosphamide)、达喀尔巴嗪(dacarbazine)、六甲蜜胺(altretamine)、异环磷酰胺(ifosfamide)、丙卡巴肼(procarbazine)、二氯甲二乙胺(mechlorethamine)、氮芥(mustine)及二氯甲基二乙胺(mechloroethamine)、链脲菌素(streptozocin)、噻替派(thiotepa);生物反应调节剂:例如卡介苗(bacillus calmette-guerin)、地尼白介素(denileukin diftitox);抗肿瘤抗生素:例如小红莓(doxorubicin)、博莱霉素(bleomycin)、道诺霉素(daunorubicin)、道诺霉素脂质体、米托蒽醌(mitoxantrone)、表柔比星(epirubicin)、埃达霉素(idarubicin)、丝裂霉素C(mitomycin C);抗微管药剂:例如雌氮芥(estramustine);组织蛋白酶K抑制剂:例如奥当卡替(odanacatib);埃坡霉素(Epothilone)类似物:例如伊沙匹隆(ixabepilone);TpoR促效剂:例如艾曲波帕(eltrombopag);抗有丝分裂药剂:例如多烯紫杉醇(docetaxel);肾上腺类固醇抑制剂:例如胺鲁米特(aminoglutethimide);抗雄激素:例如尼鲁米特(nilutamide);雄激素受体抑制剂:例如恩杂鲁胺(enzalutamide)、乙酸阿比特龙(abiraterone acetate)、奥特罗那(orteronel)、加利特隆(galeterone)及司维特奈(seviteronel)、比卡鲁胺(bicalutamide)、氟他胺(flutamide);雄激素:例如氟羟甲基睾酮(fluoxymesterone);CDK1抑制剂:例如阿昔迪布(alvocidib)、帕柏西利(palbociclib)、利波西利(ribociclib)、曲拉西利(trilaciclib)、阿贝力布(abemaciclib);促性腺素释放激素(GnRH)受体促效剂:例如亮丙立德(leuprolide)或乙酸亮丙立德;紫杉烷抗肿瘤剂:例如卡巴他赛(cabazitaxel)、拉洛他赛(larotaxel);5-HTla受体促效剂:例如扎利罗登

(xaliproden);HPV疫苗:例如GlaxoSmithKline出售的**Cervarix®**、Merck出售的**Gardasil®**;铁螯合剂:例如地拉罗司(deferasirox);抗代谢物:例如克拉屈滨(claribine)、5-氟尿嘧啶、6-硫鸟嘌呤、培美曲塞(pemetrexed)、阿糖胞苷(cytarabine)、阿糖胞苷脂质体、地西他滨(decitabine)、羟脲(hydroxyurea)、氟达拉宾(fludarabine)、氟尿苷(floxuridine)、克拉屈滨(cladribine)、甲胺喋呤(methotrexate)、喷司他汀(pentostatin);双膦酸盐:例如帕米膦酸盐(pamidronate);去甲基化药剂:例如5-阿扎胞苷、地西他滨(decitabine);抗肿瘤植物碱:例如所结合的太平洋紫杉醇蛋白质(paclitaxel protein-bound);长春碱(vinblastine)、长春新碱(vincristine)、长春瑞宾(vinorelbine)、太平洋紫杉醇(paclitaxel);类视黄素:例如亚利崔托宁(alitretinoin)、维甲酸(tretinoin)、异维甲酸(isotretinoin)、贝瑟罗汀(bexarotene);糖皮质类固醇:例如氢化可的松(hydrocortisone)、地塞米松(dexamethasone)、泼尼松龙(prednisolone)、泼尼松(prednisone)、甲基泼尼松龙(methylprednisolone);细胞介素,例如白介素-2、白介素-11(奥普瑞白介素(oprevelkin))、干扰素α(IFN-α);雌激素受体下调剂:氟维司群(fulvestrant);抗雌激素:例如他莫昔芬(tamoxifen)、托瑞米芬(toremifene);选择性雌激素受体调节剂(SERM):例如拉洛昔芬(raloxifene);促黄体生成激素释放激素(LHRH)促效剂:例如戈舍瑞林(goserelin);孕酮:例如甲地孕酮(megestrol);细胞毒性剂:三氧化二砷、天冬酰胺酶(也称为L-天冬酰胺酶、欧文菌属L-天冬酰胺酶;抗恶心药物:例如NK-1受体拮抗剂(例如卡索匹坦(casopitant));细胞保护剂:例如阿米福汀(amifostine)、甲酰四氢叶酸(leucovorin);及免疫检查点抑制剂。术语“免疫检查点”是指CD4及CD8T细胞的细胞表面上的一组分子。免疫检查点分子包括(但不限于)程序性死亡1(PD-1)、细胞毒性T淋巴球抗原4(CTLA-4)、B7H1、B7H4、OX-40、CD 137、CD40及LAG3。可充当适用于本公开的方法中的免疫检查点抑制剂的免疫治疗剂包括(但不限于)PD-L1、PD-L2、CTLA4、TIM3、LAG3、VISTA、BTLA、TIGIT、LAIR1、CD 160、2B4和/或TGFRβ的抑制剂。

[0817] 在一些实施例中,一或多种其它治疗剂是选自以下药剂:抗FGFR抗体;细胞毒性剂;靶向雌激素受体或其它内分泌疗法、免疫检查点抑制剂、CDK抑制剂、其它受体酪氨酸激酶抑制剂、BRAF抑制剂、MEK抑制剂、PI3K抑制剂、SHP2抑制剂及SRC抑制剂。(参见M.卡托(M.Katoh),《自然·综述·临床肿瘤学(Nat.Rev.Clin.Oncol.)》2019,16:105-122;蔡Y.K.(Y.K.Chae)等人,《肿瘤靶标(Oncotarget)》2017,8:16052-16074;L.富米沙诺(L.Formisano)等人,《自然·通讯(Nat.Comm.)》2019,10:1373-1386;及其中引用的参考文献)。

[0818] 以代码序号、属类或商标名标识之活性化合物的结构可获自正版标准概要“默克索引(The Merck Index)”或数据库,例如Patents International(例如IMS World Publications)。

[0819] 本发明化合物也可以与已知治疗方法(例如施用激素或辐射)组合使用。在某些实施例中,所提供的化合物用作放射增敏剂,尤其用于治疗对放射疗法展现不良灵敏性的肿瘤。

[0820] 本发明化合物可单独或与一或多种其它治疗化合物组合施用,可能的组合疗法采用的形式为本发明化合物及一或多种其它治疗化合物的固定组合或交错或彼此独立的施用,或固定组合与一或多种其它治疗化合物的组合施用。此外或另外,本发明化合物可与化

学疗法、放射疗法、免疫疗法、光疗法、手术介入或其组合进行组合，尤其用于肿瘤疗法。如上文所述，在其它治疗策略的背景下，长期疗法同样可能，辅助疗法也可以。其它可能的疗法为在肿瘤消退后维持患者状态的疗法，或甚至为化学预防疗法，例如对于风险下的患者。

[0821] 那些其它药剂可作为多次给药方案的一部分与含有本发明化合物的组合物分开施用。或者，那些药剂可为单一剂型的一部分，与本发明化合物一起混合成单一组合物。若作为多次给药方案的一部分施用，则两种活性剂可同时、依次或彼此间隔一定时间段(通常彼此间隔在五小时内)提供。

[0822] 如本文所用，如本文所用，术语“组合(combination/combined)”及相关术语是指同时或依次施用根据本发明的治疗剂。举例来说，本发明化合物可与另一治疗剂以个别单位剂型同时或依次施用或以单一单位剂型一起施用。因此，本发明提供一种包含本发明化合物、另一种治疗剂及药学上可接受的载剂、佐剂或媒剂的单一单位剂型。

[0823] 可与载剂物质组合产生单一剂型的本发明化合物及另一种治疗剂(在包含如上文所述的另一种治疗剂的那些组合物中)的量将视所治疗的宿主及特定施药模式而变化。优选地，本发明组合物应调配成使得本发明化合物的可施用剂量在每公斤体重每天0.01-100mg之间。

[0824] 在包含另一种治疗剂的那些组合物中，所述另一种治疗剂及本发明化合物可协同地起作用。因此，此类组合物中的另一种治疗剂的量将小于仅利用所述治疗剂的单一疗法中所需的量。在此类组合物中，另一种治疗剂的可施用剂量在每公斤体重每天0.01-1,000μg之间。

[0825] 存在于本发明组合物中的其它治疗剂的量将不超过通常在包含那种治疗剂作为唯一活性剂的组合物中施用的量。另一种治疗剂在本发明所公开的组合物中的量优选在通常存在于包含所述药剂作为唯一治疗活性剂的组合物中的量的约50％至100％范围内。

[0826] 本发明化合物或其医药组合物也可并入用于包覆可植入医学装置(例如假肢、人工瓣膜、血管移植物、血管内支架及导管)的组合物中。血管内支架例如已用于克服再狭窄(损伤后的血管壁再狭窄)。然而，使用血管内支架或其它可植入装置的患者具有凝块形成或血小板活化的风险。可通过用包含激酶抑制剂的药学上可接受的组合物预包覆所述装置来预防或减轻这些非所需效应。用本发明化合物包覆的可植入装置为本发明的另一实施例。

[0827] 本公开的任一种化合物和/或组合物可提供于包含所述化合物和/或组合物的试剂盒中。因此，在一些实施例中，本公开的化合物和/或组合物提供于试剂盒中。

[0828] 通过以下非限制性实例进一步描述本公开。

[0829] 实例

[0830] 本文提供实例以促进对本公开的更透彻理解。以下实例用于说明制备及实施本公开的目标的示例性方式。然而，本公开的范畴不应理解为限于这些实例中所公开的特定实施例，所述实例仅具说明性。

[0831] 如以下实例中所描绘，在某些示例性实施例中，根据以下通用程序来制备化合物。应了解，尽管通用方法描绘本发明的某些化合物的合成，但以下通用方法及本领域中的普通技术人元已知的其它方法可应用于如本文所述的这些化合物中的每一者的其它类别及子类及种类。本发明的其它化合物是通过与本文在实例中所述的方法基本上类似的方法及

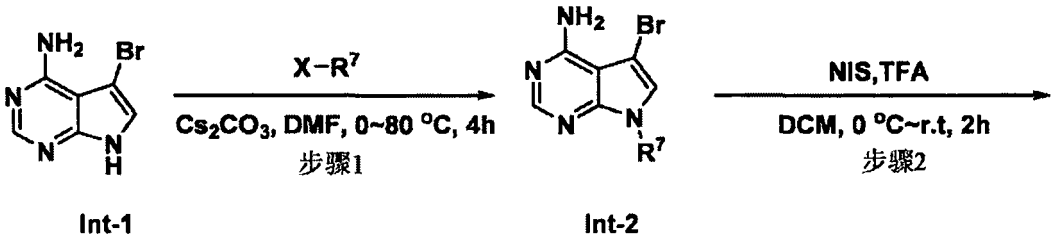
本领域中的技术人元已知的方法制备。

[0832] 在下述合成方法的描述中,除非另有说明,否则应了解,所有反应条件(例如反应溶剂、气氛、温度、持续时间及处理程序)选自标准反应条件,除非另外指明。在通用流程中,熟悉有机合成技艺的人元应了解,分子的各个部分上存在的官能基应与所提出的试剂及反应兼容。与反应条件不兼容的取代基对于本领域中的技术人元而言将为显而易见的,且因此指定替代方法(例如保护基团或替代反应的使用)。实例中的起始物质可市购或容易通过标准方法自已知物质制备。

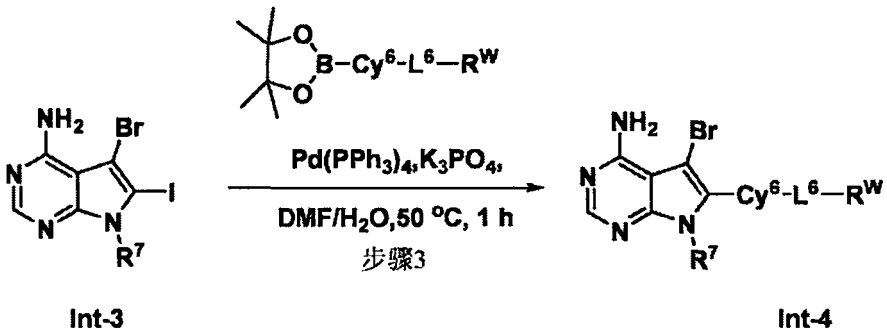
[0833] 本文中鉴别为"中间物"的至少一些化合物作为本公开的化合物涵盖在内。

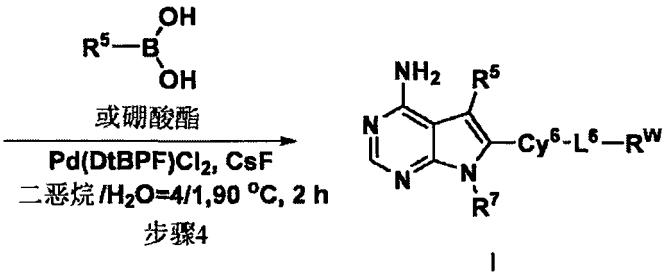
[0834] 在一些实施例中,式I化合物是根据下述流程1中所描绘的通用程序制备。

[0835] 流程1



[0836]





[0837] 在一些实施例中,步骤1包含使Int-1与式X-R^7化合物缩合,从而形成式Int-2化合物,其中R^7在本文的实施例中定义且X为离去基。

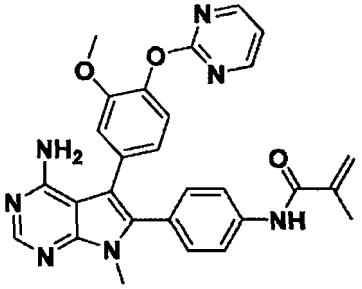
[0838] 在一些实施例中,步骤2包含使式Int-2化合物发生碘化。在一些实施例中,所用试剂为N-碘丁二酰亚胺。

[0839] 在一些实施例中,步骤3包含使式Int-3化合物与经适合反应基官能化的包含Cy^6-L^6-R^W的合成组元偶合,从而形成式Int-4化合物。在一些实施例中,适合反应基为硼酸酯。在一些实施例中,适合反应基为频哪醇硼酸酯。

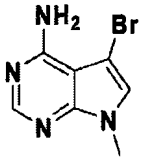
[0840] 在一些实施例中,步骤4包含使式Int-4化合物与经适合反应基官能化之包含R^5的合成组元偶合,从而形成式I化合物。在一些实施例中,适合反应基为硼酸或硼酸酯。

[0841] 实例1

[0842] N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

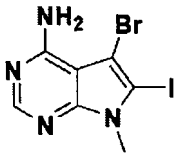
[0843] 

[0844] 5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0845] 

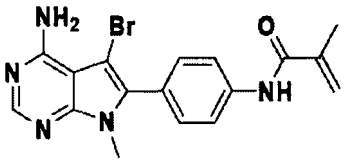
[0846] 步骤1:将5-溴-7H-吡咯并[2,3-d]嘧啶-4-胺(3g,14.0mmol)、Cs_2CO_3(9.10g,28.0mmol)、DMF(50mL)及搅拌棒。将混合物冷却至0℃且添加碘甲烷(1.98g,14.0mmol),且在0℃下搅拌溶液3小时。用H_2O(300mL)稀释反应混合物,且用EA(300mL)萃取水相三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用MeOH/DCM=1/80洗脱)纯化。真空浓缩,产生呈黄色结晶固体状的5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(2.20g,70%)。

[0847] 5-溴-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0848] 

[0849] 步骤2:向圆底烧瓶中装入5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(3g,13.2mmol)、TFA(7.52g,66.0mmol)、DCM(50mL)及搅拌棒。将混合物冷却至0℃且添加1-碘吡咯烷-2,5-二酮(2.96g,13.2mmol),且在室温下搅拌溶液2小时。用饱和Na_2SO_3溶液(100mL)稀释反应混合物。用$NaHCO_3$饱和溶液将溶液pH调节至7~8。将固体过滤且用H_2O洗涤,然后用少量DCM洗涤且产生呈白色无定形固体状的5-溴-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(3.70g,80%)。

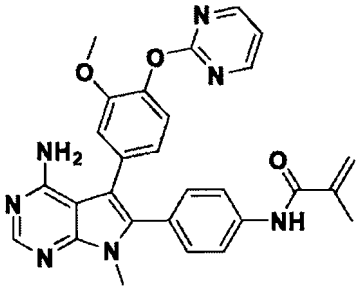
[0850] N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

[0851] 

[0852] 步骤3:向可再密封的反应瓶中装入5-溴-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(3.7g,10.51mmol)、N-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)甲基丙烯酰胺(3.7g,12.61mmol)、$Pd(PPh_3)_4$(1.21g,1.05mmol)、K_3PO_4(6.68g,31.53mmol)、DMF(50mL)、H_2O(3mL)及搅拌棒,随后抽真空并且用氮气吹扫三次。在50℃下搅拌混合物1小时。真空浓缩反应混合物。所得粗物质通过硅胶色谱(用MeOH/DCM=1/100~1/20洗脱)纯

化。真空浓缩,产生呈灰白色无定形固体状的N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(2.2g,54%)。

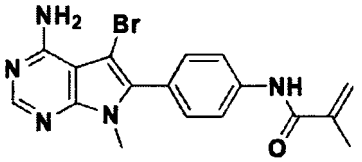
[0853] N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

[0854] 

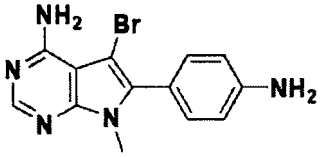
[0855] 步骤4:向可再密封的反应瓶中装入N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(120mg,0.31mmol)、2-(2-甲氧基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基)嘧啶(122mg,0.373mmol)、Pd(DtBPF)Cl_2(20.1mg,0.031mmol)、CsF(240mg,0.930mmol)、DMF(4mL)、H_2O(0.5)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物2小时。真空浓缩反应混合物。所得粗物质通过TLC(用MeOH/DCM=1/15洗脱)纯化。真空浓缩,产生呈白色无定形固体状的N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(13.9mg,9%)。

[0856] 实例2

[0857] N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺的替代途径

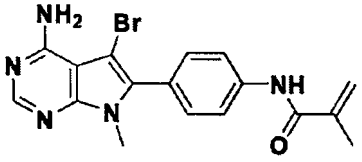
[0858] 

[0859] 6-(4-氨基苯基)-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0860] 

[0861] 步骤1:向圆底烧瓶中装入4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基氨基甲酸叔丁酯(20g,47.8mmol)、DCM(240mL)及搅拌棒。添加TFA(60mL)。在室温下搅拌溶液4小时。反应混合物用Na_2CO_3饱和水溶液(40mL)碱化,且将固体滤出且真空浓缩。由此产生呈灰白色无定形固体状的6-(4-氨基苯基)-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(14g,92.1%)。

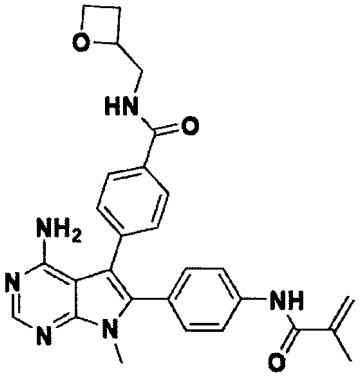
[0862] N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

[0863] 

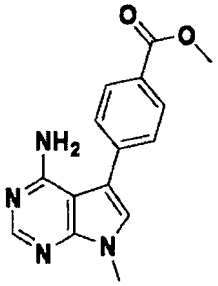
[0864] 步骤2:向可再密封的反应瓶中装入6-(4-氨基苯基)-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(10.0g,31.4mmol)、DMF/吡啶(4:1,200mL)及搅拌棒,随后抽真空且用氮气吹扫三次。且将溶液冷却至0℃。随后将甲基丙烯酰氯(4.0g,37.7mmol)溶解于DMF(10mL)中且添加至上述溶液中,且在室温下搅拌混合物1小时。反应混合物用H_2O(200mL)稀释,且水相用乙酸乙酯(200mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质用MeCN再结晶。真空浓缩,产生呈灰白色无定形固体状的N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(8.8g,73%)。

[0865] 实例3

[0866] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(氧杂环丁-2-基甲基)苯甲酰胺

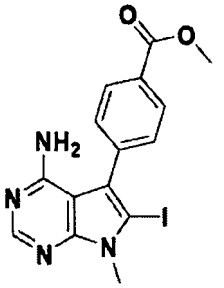
[0867] 

[0868] 4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸甲酯

[0869] 

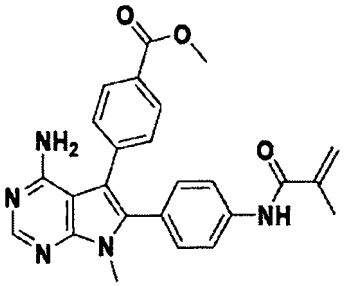
[0870] 步骤1:向可再密封的反应瓶中装入5-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(20g,72.9mmol)、[4-(甲氧基羰基)苯基]硼酸(15.7g,87.4mmol)、Pd(DtBPF)Cl_2(4.74g,7.29mmol)、CsF(33.1g,218mmol)、DMF(200mL)、H_2O(25mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物1小时。反应混合物用H_2O(500mL)稀释,且水相用DCM(200mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。向反应混合物中添加MeCN(10mL)且经由**Celite®**垫过滤,用MeCN洗涤垫。真空浓缩滤液且所得固体为4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸甲酯(11.0g,38.9mmol),以黄色无定形固体状获得。

[0871] 4-(4-氨基-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸甲酯

[0872] 

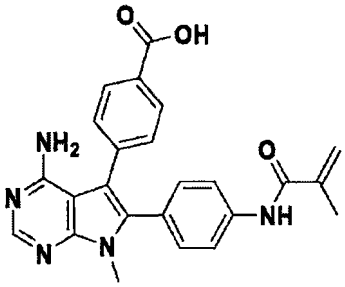
[0873] 步骤2:向圆底烧瓶中装入4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸甲酯(10.9g,38.6mmol)、DCM(200mL)、TFA(13.1g,115mmol)及搅拌棒。将混合物冷却至0℃,添加NIS(9.53g,42.4mmol),且在室温下搅拌溶液1小时。反应混合物用Na_2SO_3溶液稀释,且水相用DCM(300mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。添加DCM(20mL)且经由**Celite®**垫过滤反应混合物,用少量DCM洗涤垫。真空浓缩滤液且所得固体为4-{4-氨基-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸甲酯(12.0g,29.3mmol),以灰白色无定形固体状获得。

[0874] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸甲酯

[0875] 

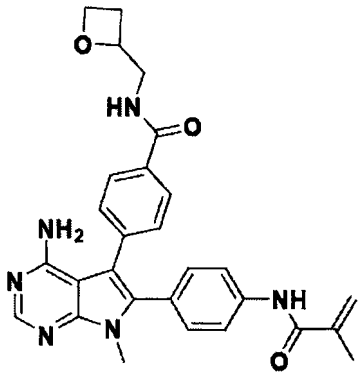
[0876] 步骤3:向可再密封的反应瓶中装入4-{4-氨基-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸甲酯(11.9g,29.1mmol)、2-甲基-N-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]丙-2-烯酰胺(10.0g,34.9mmol)、$Pd(dppf)Cl_2$(2.12g,2.91mmol)、K_3PO_4(18.5g,87.3mmol)、DMF(100mL)、H_2O(12.5mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物1小时。反应混合物用H_2O(500mL)稀释,且水相用DCM(300mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用MeOH/DCM=1/40洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的4-{4-氨基-7-甲基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸甲酯(7.70g,17.4mmol)。

[0877] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸

[0878] 

[0879] 步骤4:向圆底烧瓶中装入4-{4-氨基-7-甲基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸甲酯(7.65g,17.3mmol)、MeOH(40mL)、NaOH(2N,40mL)及搅拌棒。在室温下搅拌溶液整夜。用HCl(2M)将反应混合物的pH调节至6～7。反应混合物经由Celite®垫过滤,用H_2O洗涤垫。真空浓缩滤液且所得固体为4-{4-氨基-7-甲基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸(6.50g,15.2mmol),以灰白色无定形固体呈状获得。

[0880] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(氧杂环丁-2-基甲基)苯甲酰胺

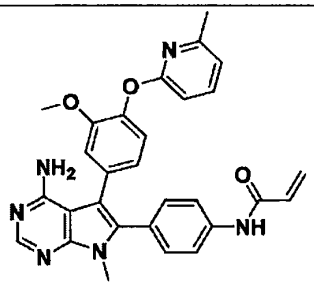
[0881] 

[0882] 步骤5:向圆底烧瓶中装入4-{4-氨基-7-甲基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}苯甲酸(60mg,0.14mmol)、1-(氧杂环丁-2-基)甲胺(13.4mg,0.15mmol)、HATU(58.7mg,0.15mmol)、DIEA(54.2mg,0.42mmol)及搅拌棒。添加二甲基甲酰胺(3mL),且在25℃下搅拌溶液2小时。所得粗物质通过HPLC纯化(柱:XBridge Prep Phenyl OBD柱,19×150mm,5μm,13nm)。冻干产生呈灰白色无定形固体状的4-{4-氨基-7-甲基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}-N-[(氧杂环丁-2-基)甲基]苯甲酰胺(20.0mg,0.040mmol)。

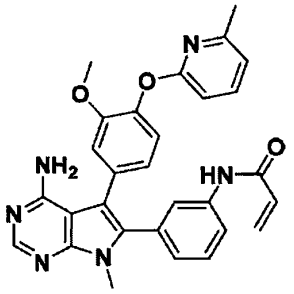
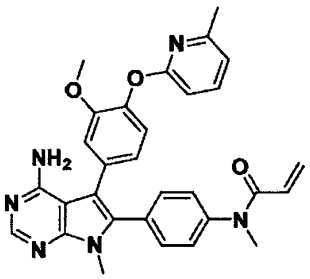
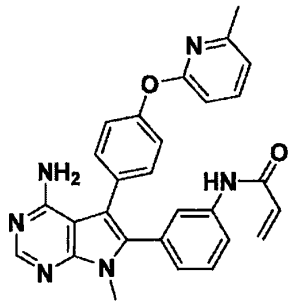
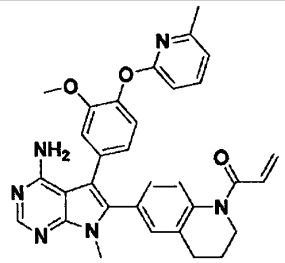
[0883] 根据实例1-3的方法制备的其它化合物描绘于下表2中。

[0884] 表2.其它的示例性吲哚化合物

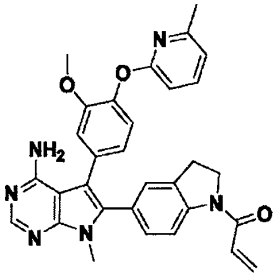
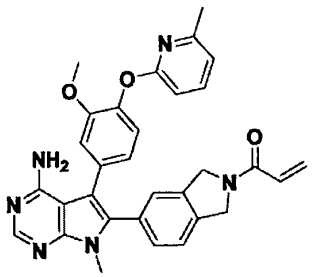
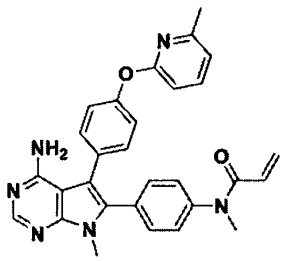
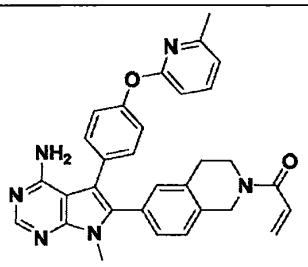
[0885]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.21 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.66 (t, J = 7.8 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.07 (d, J = 8.1 Hz, 1H), 6.98 - 6.89 (m, 2H), 6.83 (dd, J = 8.0, 2.0 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 6.06 (s, 2H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.63 (s, 3H), 3.54 (s, 3H), 2.30 (s, 3H).	507.3

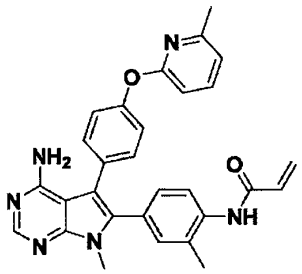
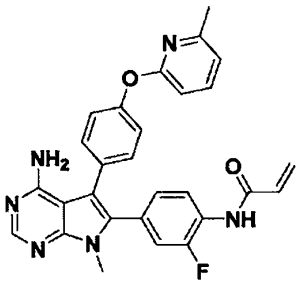
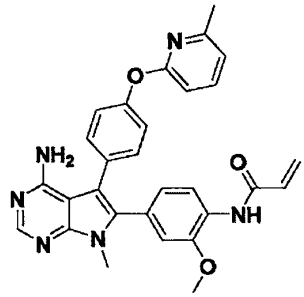
[0886]

化合物	结构	质子 NMR	MS [M+1]
N-(3-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.23 (s, 1H), 7.75 (t, J = 1.9 Hz, 1H), 7.67 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.62 (dd, J = 8.3, 7.4 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.13 (ddt, J = 13.0, 7.8, 1.0 Hz, 2H), 6.99 - 6.90 (m, 3H), 6.58 (dt, J = 8.3, 0.8 Hz, 1H), 6.48 - 6.32 (m, 2H), 5.80 (dd, J = 9.3, 2.5 Hz, 1H), 3.74 (s, 3H), 3.57 (s, 3H), 2.39 (s, 3H).	507.35
N-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-N-甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.65 (dd, J = 8.2, 7.3 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.42 - 7.34 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.01 (s, 2H), 6.96 - 6.91 (m, 2H), 6.88 (dd, J = 8.0, 2.0 Hz, 1H), 6.67 - 6.60 (m, 1H), 6.17 (dd, J = 16.8, 2.5 Hz, 1H), 6.08 (d, J = 11.3 Hz, 1H), 5.58 - 5.50 (m, 1H), 3.72 (s, 3H), 3.67(s, 3H), 3.28 (s, 3H), 2.29 (s, 3H).	521.35
N-(3-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.21 (s, 1H), 7.74 - 7.63 (m, 3H), 7.37 (t, J = 7.9 Hz, 1H), 7.33 - 7.23 (m, 2H), 7.17 - 6.97 (m, 4H), 6.75 (d, J = 8.2 Hz, 1H), 6.42 (dd, J = 16.9, 10.1 Hz, 1H), 6.26 (dd, J = 17.0, 2.1 Hz, 1H), 5.96 (s, 1H), 5.77 (dd, J = 10.0, 2.1 Hz, 1H), 3.62 (s, 3H), 2.33 (s, 3H).	477.30
1-(6-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,4-二氢喹啉-1(2H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 氯仿-d) δ 8.31 (s, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.20 (s, 1H), 7.17 - 7.08 (m, 3H), 6.88 (dd, J = 7.6, 3.0 Hz, 2H), 6.83 (d, J = 2.0 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 - 6.44 (m, 2H), 5.74 (dd, J = 9.4, 2.7 Hz, 1H), 3.90 (t, J = 6.5 Hz, 2H), 3.82 (s, 3H), 3.64 (s, 3H), 2.73 (t, J = 6.5 Hz, 2H), 2.42 (s, 3H), 2.01 (p, J = 6.5 Hz, 2H).	547.4

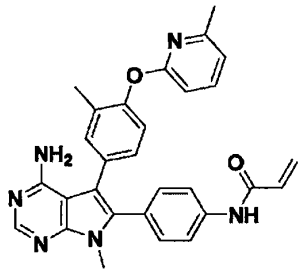
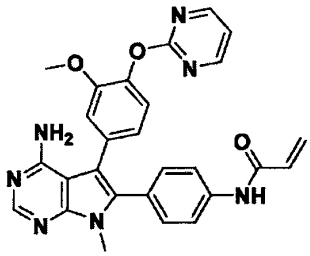
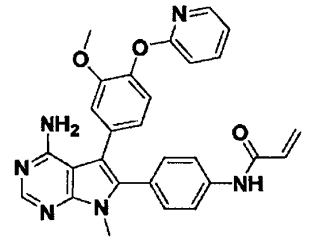
[0887]

化合物	结构	质子 NMR	MS [M+1]
1-(5-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吲哚啉-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 8.18 (s, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.29 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.85 - 6.70 (m, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.32 (d, J = 16.5 Hz, 1H), 5.88 - 5.81 (m, 1H), 4.26 (s, 2H), 3.67 (s, 3H), 3.59 (s, 3H), 3.18 (d, J = 9.0 Hz, 2H), 2.31 (s, 3H).	533.40
1-(5-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)异吲哚啉-2-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.43 (t, J = 3.9 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.07 (dd, J = 8.1, 1.0 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.81 (dd, J = 8.0, 1.6 Hz, 1H), 6.67 (ddt, J = 21.6, 8.0, 4.6 Hz, 2H), 6.23 (dt, J = 16.8, 2.2 Hz, 1H), 6.05 (s, 1H), 5.76 (ddd, J = 10.3, 3.7, 2.3 Hz, 1H), 5.00 (s, 1H), 4.95 (s, 1H), 4.73 (d, J = 17.7 Hz, 2H), 3.62 (d, J = 1.7 Hz, 3H), 3.56 (s, 3H), 2.29 (d, J = 3.6 Hz, 3H).	533.40
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-N-甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.73 (dd, J = 8.1, 7.4 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.37 - 7.22 (m, 4H), 7.14 - 6.96 (m, 3H), 6.78 (d, J = 8.1 Hz, 1H), 6.22 - 6.01 (m, 2H), 5.58 (dd, J = 9.9, 2.7 Hz, 1H), 3.65 (s, 3H), 3.27 (s, 3H), 2.33 (s, 3H).	491.15
1-(6-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,4-二氢异喹啉-2(1H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.30 - 7.15 (m, 5H), 7.13 - 7.06 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.89 (dd, J = 16.7, 10.5 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.15 (dd, J = 16.7, 2.4 Hz, 1H), 5.88 (s, 2H), 5.72 (dd, J = 10.4, 2.4 Hz, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 3.80 (d, J = 6.3 Hz, 2H), 3.62 (s, 3H), 2.83 (s, 2H), 2.33 (s, 3H).	517.25

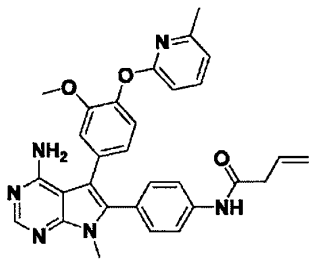
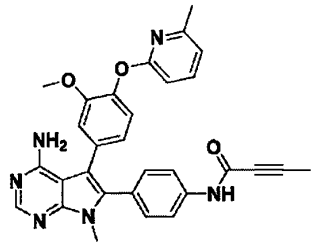
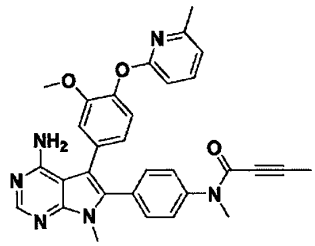
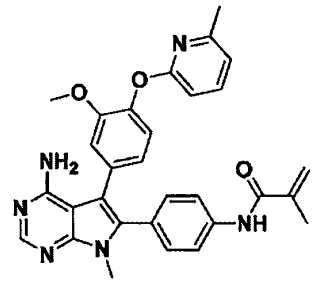
[0888]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.20 (s, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.23 (d, J = 2.0 Hz, 1H), 7.17 (dd, J = 8.3, 2.1 Hz, 1H), 7.15 - 7.07 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.57 (dd, J = 17.0, 10.2 Hz, 1H), 6.26 (dd, J = 17.0, 2.1 Hz, 1H), 6.14 - 5.86 (m, 1H), 5.77 (dd, J = 10.2, 2.0 Hz, 1H), 3.63 (s, 3H), 2.34 (s, 3H), 2.20 (s, 3H).	491.35
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氟苯基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.21 (s, 1H), 8.15 (t, J = 8.1 Hz, 1H), 7.74 (dd, J = 8.2, 7.4 Hz, 1H), 7.37 - 7.33 (m, 2H), 7.23 - 7.16 (m, 2H), 7.16 - 7.08 (m, 2H), 7.03 (dt, J = 7.4, 0.7 Hz, 1H), 6.77 (dt, J = 8.2, 0.7 Hz, 1H), 6.58 (dd, J = 17.0, 10.2 Hz, 1H), 6.42 (dd, J = 17.0, 1.8 Hz, 1H), 5.83 (dd, J = 10.2, 1.8 Hz, 1H), 3.73 (s, 3H), 2.43 (s, 3H).	495.30
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲氧基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.21 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.35 - 7.24 (m, 2H), 7.17 - 7.07 (m, 2H), 7.07 - 6.98 (m, 2H), 6.98 - 6.89 (m, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.73 (dd, J = 17.0, 10.2 Hz, 1H), 6.25 (dd, J = 17.1, 2.1 Hz, 1H), 5.92 (s, 1H), 5.73 (dd, J = 10.2, 2.1 Hz, 1H), 3.70 (d, J = 9.0 Hz, 6H), 2.34 (s, 3H).	507.35

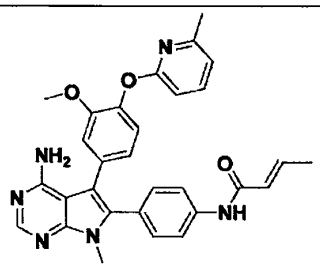
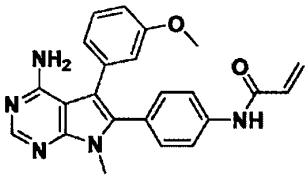
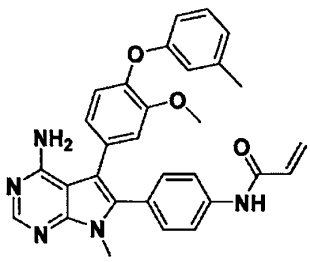
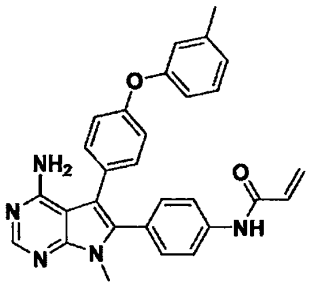
[0889]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(3-甲基-4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.77 - 7.66 (m, 3H), 7.41 - 7.30 (m, 2H), 7.21 (d, J = 2.2 Hz, 1H), 7.07 (dd, J = 8.2, 2.2 Hz, 1H), 6.97 (dd, J = 7.8, 5.7 Hz, 2H), 6.69 (d, J = 8.1 Hz, 1H), 6.45 (dd, J = 16.9, 10.1 Hz, 1H), 6.27 (dd, J = 16.9, 2.1 Hz, 1H), 5.92 (s, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.62 (s, 3H), 2.32 (s, 3H), 2.06 (s, 3H).	491.35
N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.56 (d, J = 4.8 Hz, 2H), 8.40 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.48 (s, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.05 (t, J = 4.8 Hz, 1H), 6.94 (dd, J = 8.1, 2.0 Hz, 1H), 6.86 (d, J = 1.9 Hz, 1H), 6.49 (dd, J = 16.9, 1.3 Hz, 1H), 6.29 (dd, J = 16.9, 10.2 Hz, 1H), 5.83 (dd, J = 10.2, 1.3 Hz, 1H), 5.27 (s, 2H), 3.75 (s, 3H), 3.57 (s, 3H)	494.15
N-(4-(4-氨基-5-(3-甲氧基-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.39 (s, 1H), 8.15 (ddd, J = 5.0, 2.0, 0.8 Hz, 1H), 7.72 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.44 (s, 1H), 7.30 (d, J = 1.9 Hz, 1H), 7.28 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.00 (ddd, J = 7.2, 5.0, 0.9 Hz, 1H), 6.98 - 6.89 (m, 2H), 6.86 (d, J = 2.0 Hz, 1H), 6.48 (dd, J = 16.8, 1.2 Hz, 1H), 6.28 (dd, J = 16.8, 10.2 Hz, 1H), 5.83 (dd, J = 10.2, 1.2 Hz, 1H), 5.35 (s, 2H), 3.75 (s, 3H), 3.60 (s, 3H).	493.15

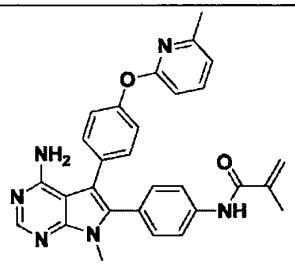
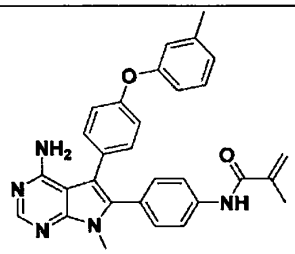
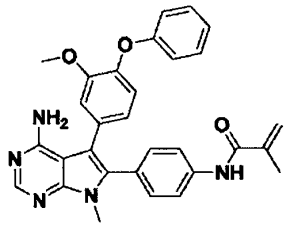
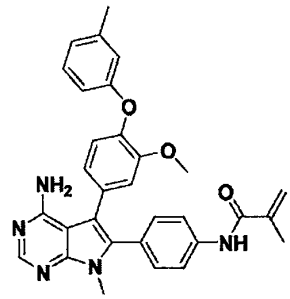
[0890]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-3-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.20 (s, 1H), 7.73 - 7.60 (m, 3H), 7.35 - 7.28 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.98 - 6.89 (m, 2H), 6.82 (dd, J = 8.1, 2.0 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.97 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H), 5.19 (dq, J = 17.2, 1.8 Hz, 1H), 5.18 - 5.10 (m, 1H), 3.61 (s, 3H), 3.54 (s, 3H), 3.14 (dt, J = 7.0, 1.5 Hz, 2H), 2.30 (s, 3H).	521.20
N-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-炔酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.20 (s, 1H), 7.70 - 7.54 (m, 3H), 7.32 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.0 Hz, 1H), 7.02 - 6.88 (m, 2H), 6.82 (dd, J = 8.2, 1.9 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.02 (s, 2H), 3.57 (d, J = 32.6 Hz, 7H), 2.30 (s, 3H), 2.06 (s, 3H).	519.35
N-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-N-甲基丁-2-炔酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.66 (dd, J = 8.2, 7.3 Hz, 1H), 7.43 (s, 4H), 7.08 (d, J = 8.0 Hz, 1H), 6.97 - 6.90 (m, 2H), 6.87 (dd, J = 8.0, 1.9 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.06 (s, 2H), 3.65 (s, 3H), 3.53 (s, 4H), 3.23 (s, 2H), 2.30 (s, 3H), 2.11 (s, 1H), 1.66 (s, 2H).	533.40
N-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.21 (s, 1H), 7.77 - 7.70 (m, 2H), 7.70 - 7.62 (m, 1H), 7.36 - 7.29 (m, 2H), 7.07 (d, J = 8.1 Hz, 1H), 6.99 - 6.89 (m, 2H), 6.82 (dd, J = 8.1, 1.9 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.62 (s, 3H), 3.55 (s, 3H), 2.30 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	521.35

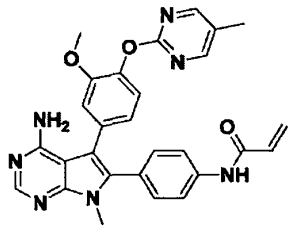
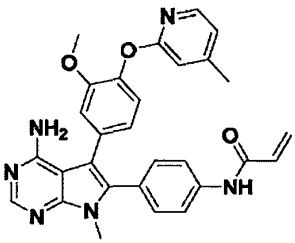
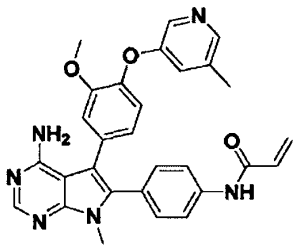
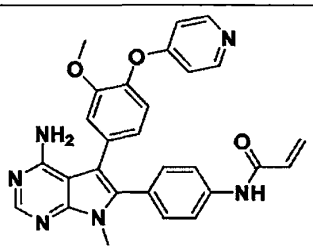
[0891]

化合物	结构	质子 NMR	MS [M+1]
(E)-N-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (d, J = 5.7 Hz, 1H), 8.20 (s, 1H), 7.66 (ddd, J = 21.5, 8.6, 3.9 Hz, 3H), 7.32 (dd, J = 8.7, 3.2 Hz, 2H), 7.07 (dd, J = 8.0, 1.7 Hz, 1H), 6.98 - 6.89 (m, 2H), 6.88 - 6.75 (m, 2H), 6.64 (d, J = 8.2 Hz, 1H), 6.13 (dd, J = 15.1, 2.0 Hz, 1H), 6.0 (m, 1H), 5.25 - 5.10 (m, 1H), 3.62 (d, J = 3.0 Hz, 3H), 3.54 (s, 3H), 3.14 (dt, J = 6.8, 1.6 Hz, 1H), 2.30 (s, 3H), 1.88 (dd, J = 6.9, 1.6 Hz, 2H)	521.35
N-(4-(4-氨基-5-(3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.19 (s, 1H), 7.72 - 7.64 (m, 2H), 7.34 - 7.24 (m, 3H), 6.90 - 6.78 (m, 2H), 6.76 (dd, J = 2.6, 1.6 Hz, 1H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 3H), 3.67 (s, 3H), 3.60 (s, 3H).	400.1
N-(4-(4-氨基-5-(3-甲氧基-4-(间甲苯基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		. ^{1}H NMR (400 MHz, DMSO-d_6) δ10.30 (s, 1H), 8.20 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 8.0 Hz, 1H), 6.90 - 6.97 (m, 2H), 6.76 - 6.88 (m, 2H), 6.71 (d, J = 2.0 Hz, 1H), 6.66-6.64 (m, 1H), 6.47-6.40 (m, 1H), 6.29-6.25 (m, 1H), 5.79-5.76 (m, 1H), 3.60 (d, J = 18.0 Hz, 6H), 2.27 (s, 3H).	506.35
N-(4-(4-氨基-7-甲基-5-(4-(间甲苯基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.19 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.35 - 7.17 (m, 6H), 7.02 - 6.80 (m, 5H), 6.44 (dd, J = 16.8, 10.0 Hz, 1H), 6.27 (dd, J = 16.8, 2.0 Hz, 1H), 6.16 - 5.66 (m, 2H), 3.61 (s, 3H), 2.30 (s, 3H).	476.15

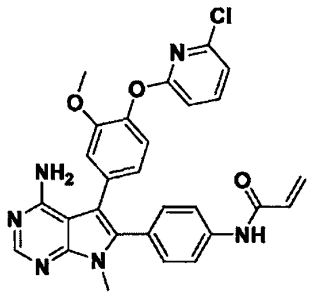
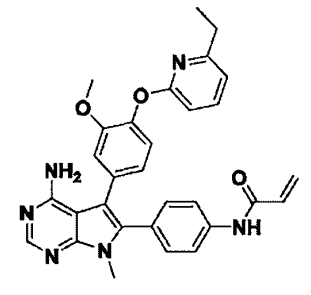
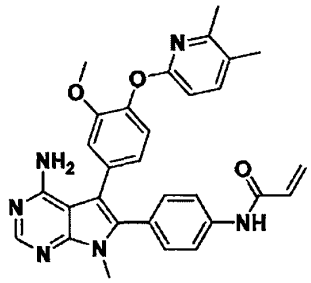
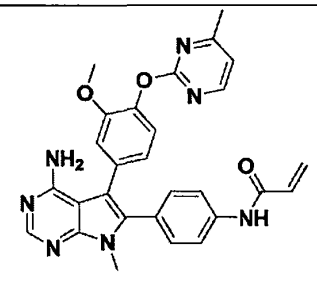
[0892]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.73 (t, J = 8.1 Hz, 3H), 7.33 - 7.22 (m, 4H), 7.13 - 7.05 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.80 (t, J = 1.0 Hz, 1H), 5.53 (t, J = 1.4 Hz, 1H), 3.62 (s, 3H), 3.32 (d, J = 0.7 Hz, 1H), 2.35 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	491.2
N-(4-(4-氨基-7-甲基-5-(4-(间甲苯基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.19 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.25 (dd, J = 18.4, 7.8 Hz, 5H), 6.95 (d, J = 8.2 Hz, 3H), 6.91 - 6.82 (m, 2H), 5.86 (s, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.61 (s, 3H), 2.30 (s, 3H), 1.95 (s, 3H).	490.15
N-(4-(4-氨基-5-(3-甲氧基-4-苯氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.20 (s, 1H), 7.77 - 7.69 (m, 2H), 7.37 - 7.27 (m, 4H), 7.04 (t, J = 7.4 Hz, 1H), 7.00 - 6.93 (m, 2H), 6.93 - 6.86 (m, 2H), 6.80 (dd, J = 8.2, 2.0 Hz, 1H), 6.06 (s, 1H), 5.81 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 3.60 (d, J = 10.8 Hz, 6H), 1.95 (d, J = 1.4 Hz, 3H).	506.20
N-(4-(4-氨基-5-(3-甲氧基-4-(间甲苯基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.20 (s, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.9 Hz, 1H), 6.98 - 6.90 (m, 2H), 6.85 (d, J = 7.5 Hz, 1H), 6.79 (dd, J = 8.1, 1.9 Hz, 1H), 6.71 (d, J = 2.3 Hz, 1H), 6.65 (dd, J = 8.2, 2.5 Hz, 1H), 6.04 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.60 (d, J = 12.6 Hz, 6H), 2.27 (s, 3H), 1.95 (s, 3H).	519.23

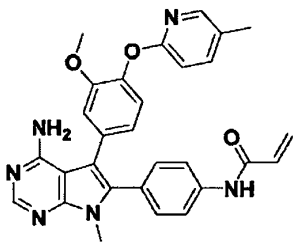
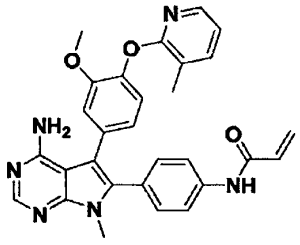
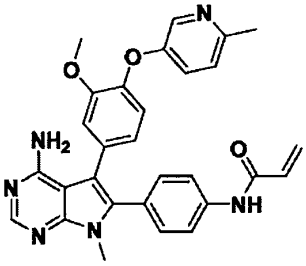
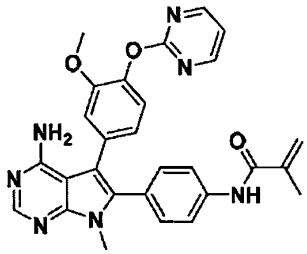
[0893]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-((5-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.29 (s, 1H), 8.44 (d, J = 0.8 Hz, 2H), 8.21 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 1.6 Hz, 1H), 6.86 (dd, J = 8.0, 2.0 Hz, 1H), 6.45 (dd, J = 16.8, 10.0 Hz, 1H), 6.32 - 6.21 (m, 1H), 5.79 (d, J = 11.6 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 2.20 (s, 3H).	508.20
N-(4-(4-氨基-5-(3-甲氧基-4-((4-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.30 (s, 1H), 8.44 (s, 2H), 8.22 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 10.0 Hz, 1H), 6.46 (dd, J = 17.2, 10.0 Hz, 1H), 6.29 (d, J = 18.8 Hz, 1H), 5.79 (d, J = 12.0 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 2.20 (s, 3H).	507.25
N-(4-(4-氨基-5-(3-甲氧基-4-(5-甲基吡啶-3-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.20 (s, 1H), 8.17 - 8.10 (m, 1H), 8.05 (d, J = 2.7 Hz, 1H), 7.78 - 7.66 (m, 2H), 7.38 - 7.26 (m, 2H), 7.12 (d, J = 2.5 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 1.9 Hz, 1H), 6.81 (dd, J = 8.1, 1.9 Hz, 1H), 6.45 (dd, J = 16.9, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 2H), 3.60 (d, J = 16.1 Hz, 6H), 2.27 (s, 3H).	507.15
N-(4-(4-氨基-5-(3-甲氧基-4-(吡啶-4-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.29 (s, 1H), 8.41 (d, J = 5.5 Hz, 2H), 8.21 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.95 - 6.79 (m, 3H), 6.52 - 6.38 (m, 1H), 6.36 - 6.20 (m, 1H), 6.14 (s, 2H), 5.86 - 5.70 (m, 1H), 3.63 (s, 3H), 3.57 (s, 3H).	493.15

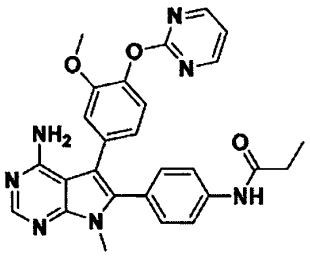
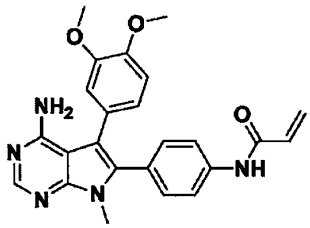
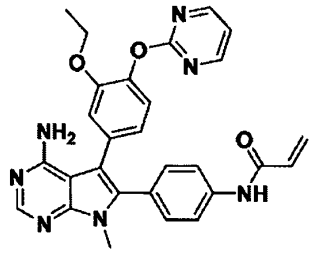
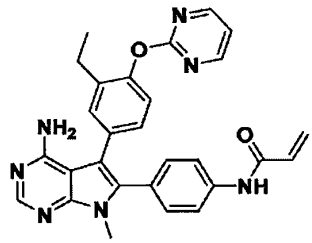
[0894]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((6-氯吡啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ10.28 (s, 1H), 8.21 (s, 1H), 7.84(t, J = 14.6 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.85 (dd, J = 6.0 Hz, 1H), 6.41 - 6.43 (m, 1H), 6.25 - 6.29 (m, 1H), 5.82 - 6.18 (br, 1H), 3.62 (s, 3H), 3.55 (s, 3H), 2.78 (t, J = 12.0 Hz, 1H).	527.30
N-(4-(4-氨基-5-(4-((6-乙基吡啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.39 (s, 1H), 7.61 (dd, J = 26.2, 7.9 Hz, 3H), 7.47 (s, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 25.9 Hz, 3H), 6.62 (d, J = 8.3 Hz, 1H), 6.48 (d, J = 16.9 Hz, 1H), 6.29 (t, J = 13.8 Hz, 1H), 5.82 (d, J = 10.2 Hz, 1H), 5.22 (s, 2H), 3.76 (s, 3H), 3.59 (s, 3H), 2.69 (d, J = 8.0 Hz, 2H), 1.20 (t, J = 7.7 Hz, 3H).	521.2
N-(4-(4-氨基-5-(4-((5,6-二甲基吡啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.20 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.81 (dd, J = 8.2, 1.8 Hz, 1H), 6.57 (d, J = 8.2 Hz, 1H), 6.45 (dd, J = 17.0, 10.0 Hz, 1H), 6.32 - 6.23 (m, 1H), 5.78 (d, J = 11.8 Hz, 1H), 3.62 (s, 3H), 3.54 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 1.24 (s, 1H).	521.20
N-(4-(4-氨基-5-(3-甲氧基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.41 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.40 - 7.33 (m, 2H), 7.17 - 7.07 (m, 2H), 6.97 (d, J = 1.8 Hz, 1H), 6.86 (dd, J = 8.0, 2.0 Hz, 1H), 6.45 (dd, J = 17.0, 10.2 Hz, 1H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 5.78 (dd, J = 10.2, 2.0 Hz, 1H), 3.61 (s, 3H), 3.53 (s, 3H), 2.40 (s, 3H).	508.15

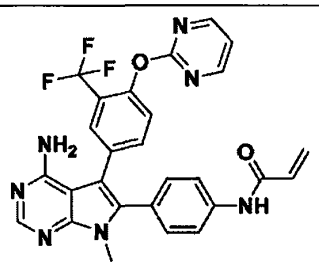
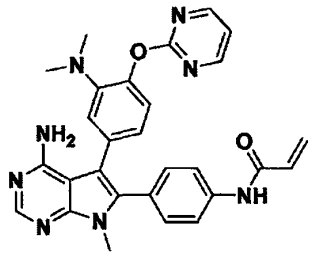
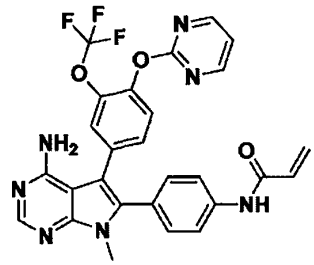
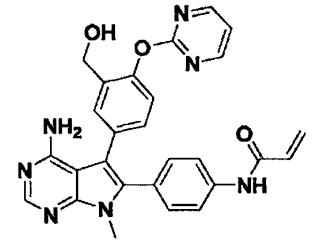
[0895]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-(5-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.71 - 7.73 (d, J = 8 Hz, 2H), 7.60 - 7.62 (d, J = 8 Hz, 1H), 7.34 - 7.36 (d, J = 8 Hz, 1H), 7.05-7.07 (d, J = 8 Hz, 1H), 6.94 (s, 1H), 6.82-6.86 (m, 2H), 6.41-6.48 (m, 1H), 6.25-6.30 (m, 1H), 5.97 (s, 1H), 5.77-5.79 (d, J = 8 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 2.21 (s, 3H).	507.35
N-(4-(4-氨基-5-(3-甲氧基-4-((3-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.21 (s, 1H), 7.88 (d, J = 4.9 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 7.2 Hz, 1H), 7.35 (dd, J = 17.4, 8.2 Hz, 2H), 7.08 (dd, J = 8.1, 2.8 Hz, 1H), 7.01 - 6.92 (m, 2H), 6.88 - 6.80 (m, 1H), 6.45 (dd, J = 17.0, 10.0 Hz, 1H), 6.28 (dd, J = 16.9, 2.0 Hz, 1H), 5.99 (s, 2H), 5.78 (dd, J = 9.9, 2.1 Hz, 1H), 3.60 (d, J = 5.7 Hz, 3H), 3.53 (s, 3H), 2.30 (s, 3H).	507.2
N-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-3-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.20 (s, 1H), 8.13 (dd, J = 2.4, 1.2 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.38 - 7.27 (m, 2H), 7.26 - 7.16 (m, 2H), 7.06 - 6.93 (m, 2H), 6.79 (dd, J = 8.0, 2.0 Hz, 1H), 6.45 (dd, J = 17.2, 10.0 Hz, 1H), 6.28 (dd, J = 17.2, 2.0 Hz, 1H), 6.05 (s, 1H), 5.78 (dd, J = 10.0, 2.0 Hz, 1H), 3.62 (s, 3H), 3.59 (s, 3H), 2.42 (s, 3H).	507.35
N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.62 (d, J = 4.8 Hz, 2H), 8.21 (s, 1H), 7.79 - 7.72 (m, 2H), 7.39 - 7.33 (m, 2H), 7.23 (t, J = 4.8 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 1.9 Hz, 1H), 6.86 (dd, J = 8.0, 2.0 Hz, 1H), 6.01 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 1.96 (s, 3H).	508.30

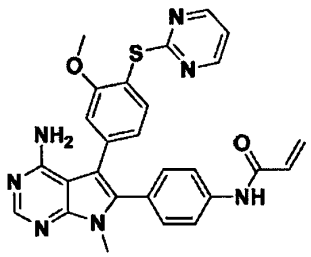
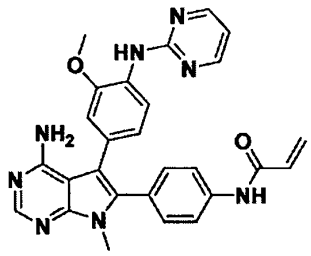
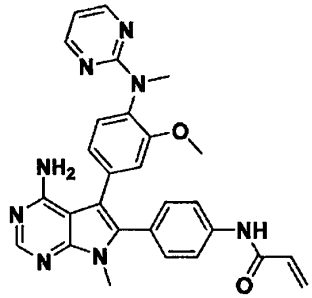
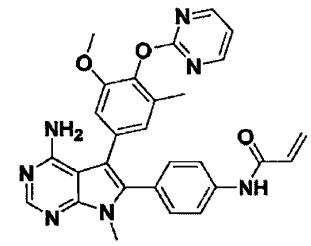
[0896]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.62 (d, J = 4.8 Hz, 2H), 8.21 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 4.8 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.0, 1.9 Hz, 1H), 5.97 (s, 2H), 3.56 (d, J = 17.7 Hz, 6H), 2.33 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H).	496.3
N-(4-(4-氨基-5-(3,4-二甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.18 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.35 - 7.23 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.45 (dd, J = 17.2, 10.0 Hz, 1H), 6.28 (dd, J = 16.8, 2.0 Hz, 1H), 5.78 (dd, J = 10.0, 2.0 Hz, 1H), 3.75 (s, 3H), 3.60 (d, J = 0.8 Hz, 6H).	430.30
N-(4-(4-氨基-5-(3-乙氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.29 (s, 1H), 8.62 (d, J = 4.8 Hz, 2H), 8.21 (s, 1H), 7.85 - 7.68 (m, 2H), 7.56 - 7.29 (m, 2H), 7.23 (t, J = 4.8 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.91 - 6.81 (m, 1H), 6.51 - 6.39 (m, 1H), 6.35 - 6.21 (m, 1H), 5.98 (s, 2H), 5.82 - 5.73 (m, 1H), 3.88 - 3.74 (m, 2H), 3.60 (s, 3H), 0.93 (t, J = 7.0 Hz, 3H).	508.35
N-(4-(4-氨基-5-(3-乙基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.65 (d, J = 4.8 Hz, 2H), 8.21 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.30 - 7.18 (m, 2H), 7.18 - 7.03 (m, 2H), 6.45 (dd, J = 16.9, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.1 Hz, 1H), 5.96 (s, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.60 (s, 3H), 2.47 - 2.31 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H).	492.15

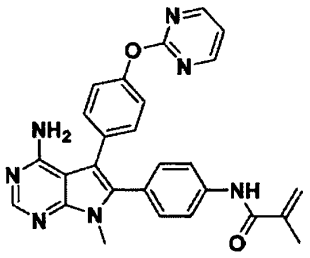
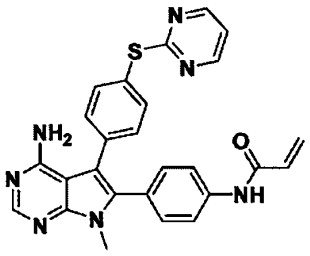
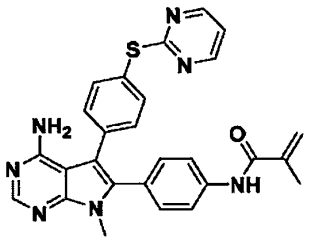
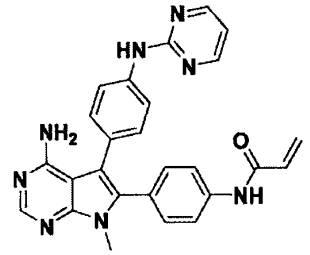
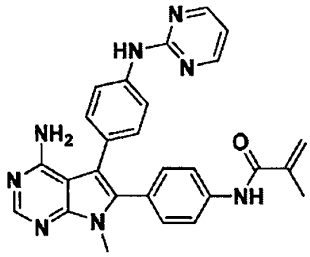
[0897]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)-3-(三氟甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.72 - 8.66 (m, 2H), 8.23 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.59 - 7.53 (m, 2H), 7.43 (d, J = 9.0 Hz, 1H), 7.39 - 7.30 (m, 3H), 6.45 (dd, J = 16.9, 10.1 Hz, 1H), 6.28 (dd, J = 16.7, 2.0 Hz, 1H), 6.03 (s, 2H), 5.83 - 5.75 (m, 1H), 3.59 (s, 3H).	532.1
N-(4-(4-氨基-5-(3-(二甲基氨基)-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.63 (d, J = 4.8 Hz, 2H), 8.20 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.39 - 7.31 (m, 2H), 7.24 (t, J = 4.8 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.89 - 6.81 (m, 2H), 6.45 (dd, J = 16.8, 10.2 Hz, 1H), 6.28 (dd, J = 16.8, 2.2 Hz, 1H), 6.06 (s, 2H), 5.78 (dd, J = 10.0, 2.2 Hz, 1H), 3.60 (s, 3H), 2.53 (s, 6H).	507.20
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)-3-(三氟甲氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.68 (d, J = 4.7 Hz, 2H), 8.23 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.40 - 7.19 (m, 6H), 6.53 - 6.36 (m, 1H), 6.30 (d, J = 2.0 Hz, 1H), 6.03 (s, 2H), 5.85 - 5.73 (m, 1H), 3.60 (s, 3H).	548.25
N-(4-(4-氨基-5-(3-(羟基甲基)-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 10.04 (s, 1H), 8.52 (dd, J = 4.2, 2.8 Hz, 1H), 8.16 (s, 1H), 8.02 (dd, J = 6.5, 2.8 Hz, 1H), 7.69 - 7.62 (m, 2H), 7.26 - 7.19 (m, 2H), 6.98 (d, J = 7.9 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.46 (dd, J = 16.9, 10.1 Hz, 1H), 6.39 (dd, J = 6.5, 4.1 Hz, 1H), 6.29 (dd, J = 16.9, 2.1 Hz, 1H), 5.79 (dd, J = 10.1, 2.1 Hz, 1H), 4.91 (s, 2H), 3.58 (s, 3H).	494.3

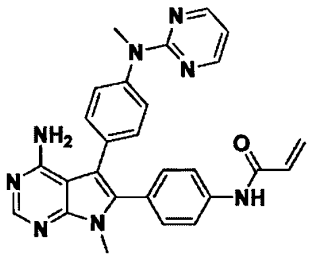
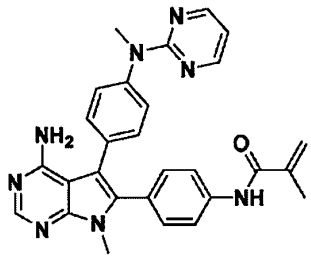
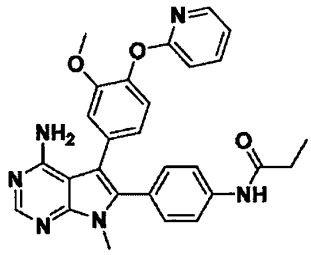
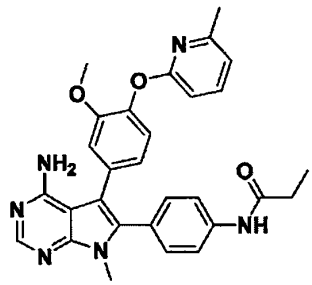
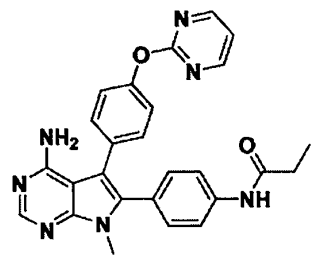
[0898]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基硫基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.30 (s, 1H), 8.57 (d, J = 4.8 Hz, 2H), 8.23 (s, 1H), 7.81 - 7.70 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.44 - 7.32 (m, 2H), 7.20 (m, J = 4.8 Hz, 1H), 7.01 - 6.83 (m, 2H), 6.46 (dd, J = 17.2, 10.0 Hz, 1H), 6.29 (dd, J = 17.2, 2.0 Hz, 1H), 6.02 (s, 1H), 5.79 (dd, J = 10.0, 2.0 Hz, 1H), 3.60 (d, J = 17.2 Hz, 6H).	510.10
N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氨基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.46-8.47 (d, J = 4.8 Hz, 1H), 8.16-8.19 (m, 2H), 8.04 (s, 1H), 7.69 - 7.71 (d, J = 8 Hz, 2H), 7.33-7.35 (d, J = 8 Hz, 2H), 6.83-6.87 (m, 3H), 6.40-6.49 (m, 1H), 6.24-6.29 (m, 1H), 5.98 (s, 1H), 5.76-5.78 (m, 1H), 3.70 (s, 3H), 3.60 (s, 3H).	493.30
N-(4-(4-氨基-5-(3-甲氧基-4-(甲基(嘧啶-2-基)氨基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.29-8.31 (m, 2H), 8.19 (s, 1H), 7.75-7.77 (d, J = 8.2 Hz, 2H), 7.19-7.21 (d, J = 8.1 Hz, 1H), 6.85-6.92 (m, 2H), 6.64 - 6.69 (m, 1H), 6.42-6.49(m, 1H), 6.25-6.31 (m, 1H), 6.01 (s, 1H), 5.77-5.80 (m, 1H), 3.56-3.59 (m, 6H), 3.30 (s, 3H).	507.35
N-(4-(4-氨基-5-(3-甲氧基-5-甲基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.29 (s, 1H), 8.61 (d, J = 4.8 Hz, 2H), 8.21 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.22 (t, J = 4.8 Hz, 1H), 6.85 - 6.77 (m, 2H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 16.9, 2.0 Hz, 1H), 5.78 (dd, J = 10.1, 2.0 Hz, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 2.05 (s, 3H).	508.25

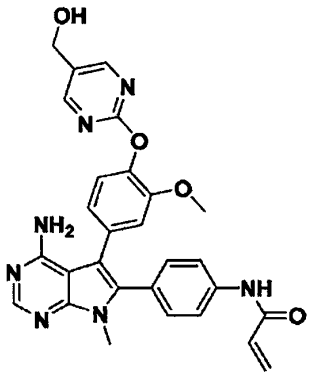
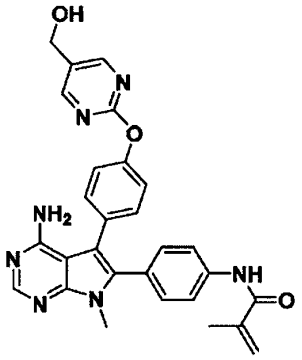
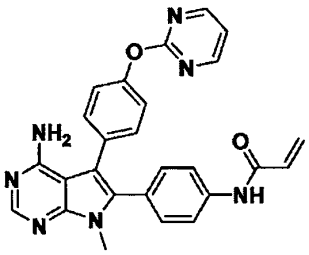
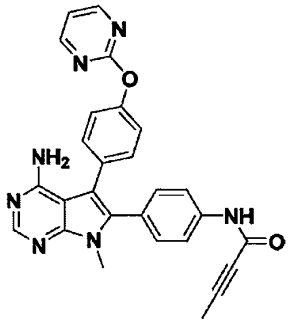
[0899]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.67 (d, J = 4.8 Hz, 2H), 8.21 (s, 1H), 7.78 - 7.70 (m, 2H), 7.35 - 7.25 (m, 5H), 7.25 - 7.17 (m, 2H), 5.83 - 5.78 (m, 1H), 5.56 - 5.51 (m, 1H), 3.60 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	478.10
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基硫基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.61 (d, J = 4.8 Hz, 2H), 8.22 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H), 7.36 - 7.29 (m, 4H), 7.25 (t, J = 4.8 Hz, 1H), 6.44 (dd, J = 17.0, 10.2 Hz, 1H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.61 (s, 3H).	480.25
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基硫基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.62 (d, J = 4.9 Hz, 2H), 8.22 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H), 7.37 - 7.28 (m, 4H), 7.25 (t, J = 4.8 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.61 (s, 3H), 1.95 (s, 3H).	494.25
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氨基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.73 (s, 1H), 8.48 (d, J = 4.8 Hz, 2H), 8.18 (s, 1H), 7.76 (d, J = 8.3 Hz, 4H), 7.68 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 6.84 (t, J = 4.7 Hz, 1H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.77 (dd, J = 10.0, 2.1 Hz, 2H), 3.61 (s, 4H).	463.25
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氨基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.73 (s, 1H), 8.48 (d, J = 4.6 Hz, 2H), 8.19 (s, 1H), 8.02 - 7.52 (m, 5H), 7.22 (dd, J = 53.0, 7.6 Hz, 4H), 6.85 (s, 1H), 5.79 (s, 2H), 5.53 (s, 1H), 3.61 (s, 3H), 1.95 (s, 3H).	477.30

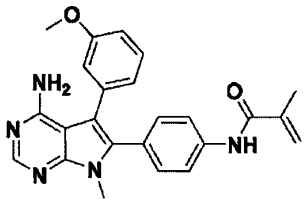
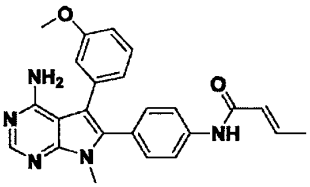
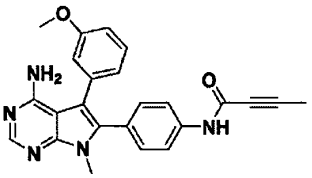
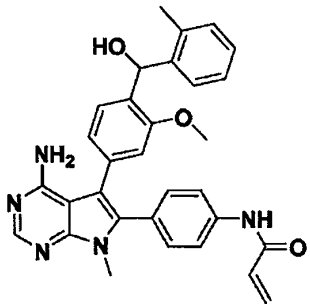
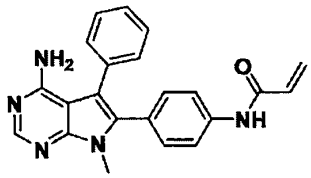
[0900]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(甲基(嘧啶-2-基)氨基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.39 (d, J = 4.8 Hz, 2H), 8.20 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.42 - 7.32 (m, 4H), 7.26 (d, J = 8.2 Hz, 2H), 6.75 (t, J = 4.7 Hz, 1H), 6.44 (dd, J = 16.9, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.0 Hz, 1H), 5.78 (dd, J = 9.9, 2.0 Hz, 2H), 3.59 (s, 3H), 3.47 (s, 3H).	477.25
N-(4-(4-氨基-7-甲基-5-(4-(甲基(嘧啶-2-基)氨基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.40 (d, J = 4.7 Hz, 2H), 8.20 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 8.9 Hz, 4H), 7.26 (d, J = 8.3 Hz, 2H), 6.75 (t, J = 4.7 Hz, 1H), 5.80 (s, 2H), 5.54 (s, 1H), 3.59 (s, 3H), 3.47 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H).	491.30
N-(4-(4-氨基-5-(3-甲氧基-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.01 (s, 1H), 8.21 (s, 1H), 8.11 (dd, J = 5.0, 1.9 Hz, 1H), 7.84 - 7.76 (m, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.13 - 7.03 (m, 2H), 6.98 - 6.92 (m, 2H), 6.83 (dd, J = 8.0, 2.0 Hz, 1H), 5.99 (s, 2H), 3.59 (s, 3H), 3.54 (s, 3H), 2.34 (q, J = 7.6 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H).	494.21
N-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.20 (s, 1H), 7.64 (d, J = 8.5 Hz, 3H), 7.30 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.98 - 6.89 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.01 (s, 2H), 3.61 (s, 3H), 3.54 (s, 3H), 2.32 (d, J = 14.9 Hz, 5H), 1.09 (t, J = 7.5 Hz, 3H).	508.22
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.67 (d, J = 4.8 Hz, 2H), 8.20 (s, 1H), 7.67 - 7.60 (m, 2H), 7.33 - 7.25 (m, 5H), 7.24 - 7.17 (m, 2H), 5.90 (s, 2H), 3.59 (s, 3H), 2.33 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.6 Hz, 3H).	466.25

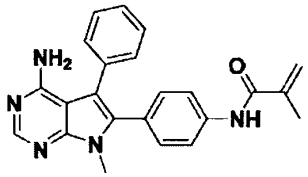
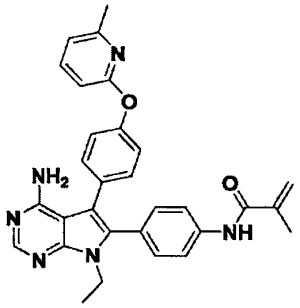
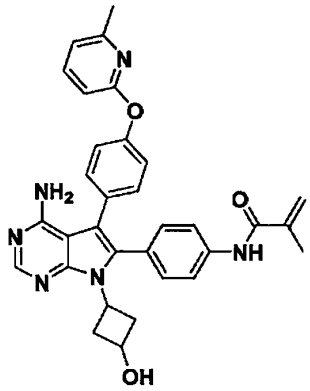
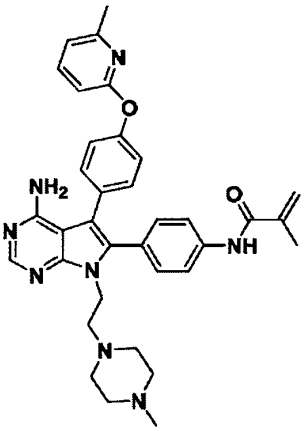
[0901]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((5-(羟基甲基)嘧啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d4) δ 8.57 (s, 2H), 8.22 (s, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.35 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.00 - 6.92 (m, 2H), 6.47 (dd, J = 17.0, 9.4 Hz, 1H), 6.39 (dd, J = 17.2, 2.5 Hz, 1H), 5.81 (dd, J = 9.5, 2.4 Hz, 1H), 4.63 (s, 2H), 3.72 (s, 3H), 3.57 (s, 3H).	524.30
N-(4-(4-氨基-5-(4-(5-(羟基甲基)嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.59 (s, 2H), 8.21 (s, 1H), 7.78 - 7.71 (m, 2H), 7.36 - 7.25 (m, 4H), 7.22 - 7.14 (m, 2H), 5.80 (t, J = 1.1 Hz, 2H), 5.54 (t, J = 1.5 Hz, 1H), 5.38 (t, J = 5.6 Hz, 1H), 4.49 (d, J = 5.5 Hz, 2H), 3.60 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H).	508.30
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.67 (d, J = 4.8 Hz, 2H), 8.21 (s, 1H), 7.75 - 7.67 (m, 2H), 7.38 - 7.25 (m, 5H), 7.25 - 7.17 (m, 2H), 6.44 (dd, J = 16.8, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.2 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.60 (s, 3H).	464.15
N-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-炔酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.67 (d, J = 4.8 Hz, 2H), 8.20 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.36 - 7.25 (m, 5H), 7.21 (d, J = 8.4 Hz, 2H), 5.89 (s, 2H), 3.59 (s, 3H), 2.07 (d, J = 9.3 Hz, 3H).	476.2

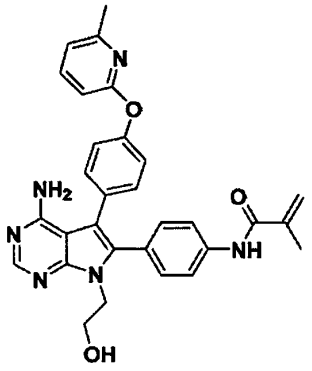
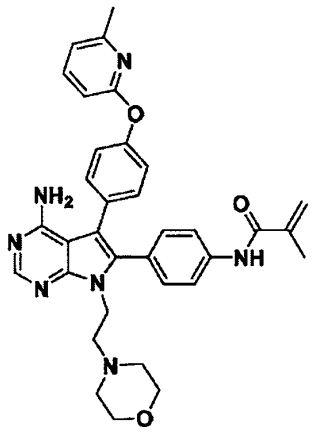
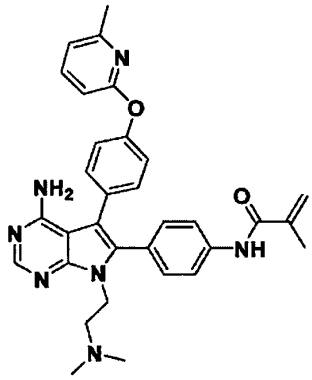
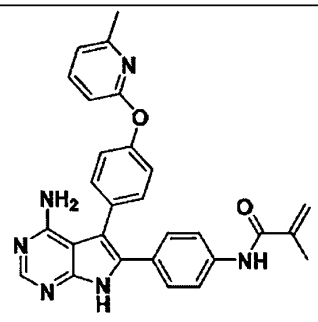
[0902]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.19 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.27 (dd, J = 8.2, 5.8 Hz, 3H), 6.86 (dd, J = 8.3, 2.6 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.77 (t, J = 2.0 Hz, 1H), 5.78 (s, 2H), 5.53 (s, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 1.95 (s, 3H).	414.1
(E)-N-(4-(4-氨基-5-(3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.19 (s, 1H), 7.70 - 7.62 (m, 2H), 7.32 - 7.24 (m, 3H), 6.90 - 6.74 (m, 4H), 6.17 - 6.08 (m, 1H), 5.91 (s, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 1.88 (dd, J = 6.8, 1.6 Hz, 3H).	414.15
N-(4-(4-氨基-5-(3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-炔酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.19 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.27 (dd, J = 8.4, 6.4 Hz, 3H), 6.86 (dd, J = 8.4, 2.8 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.78 - 6.73 (m, 1H), 5.91 (s, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 2.06 (s, 3H).	412.25
N-(4-(4-氨基-5-(4-(羟基(邻甲苯基)甲基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.22 (s, 1H), 7.71-7.43 (d, J = 8 Hz, 1H), 7.22-7.43 (m, 7H), 6.46-6.48 (m, J = 8 Hz, 1H), 6.26-6.44 (m, 2H), 5.77-5.80 (d, J = 8 Hz, 1H), 3.62 (s, 3H), 3.43 (s, 3H), 2.35 (s, 3H).	518.20
N-(4-(4-氨基-7-甲基-5-苯基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.20 (s, 1H), 7.67 (d, J = 8.7 Hz, 2H), 7.37 (dd, J = 8.1, 6.6 Hz, 2H), 7.34 - 7.18 (m, 5H), 6.43 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.1, 2.0 Hz, 1H), 3.61 (s, 3H).	370.25

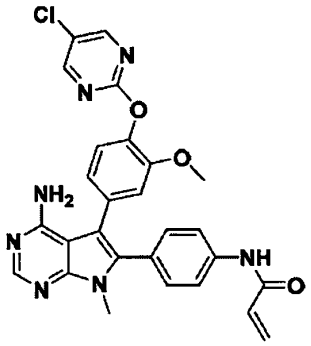
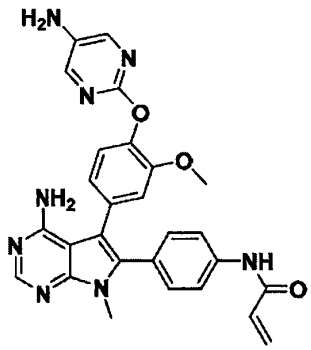
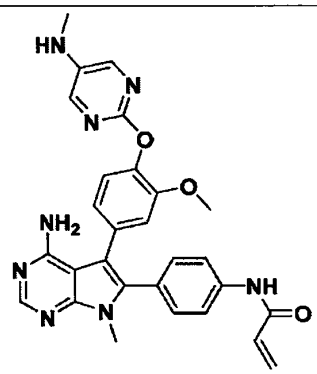
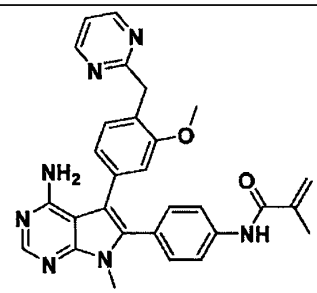
[0903]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-苯基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.19 (s, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.30 - 7.18 (m, 5H), 5.79 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	384.20
N-(4-(4-氨基-7-乙基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.20 (s, 1H), 7.73 (dd, J = 8.3, 6.6 Hz, 3H), 7.33 - 7.22 (m, 4H), 7.11 - 7.04 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 5.88 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 4.12 (q, J = 7.0 Hz, 2H), 2.34 (s, 3H), 1.95 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H).	505.2
N-(4-(4-氨基-7-(3-羟基环丁基)-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.83 - 7.66 (m, 3H), 7.22 (t, J = 8.2 Hz, 5H), 7.11 - 6.95 (m, 4H), 6.77 (d, J = 8.1 Hz, 1H), 5.79 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 5.22 (d, J = 5.8 Hz, 1H), 4.33 - 4.00 (m, 1H), 3.82 (h, J = 7.0 Hz, 1H), 3.10 - 2.90 (m, 2H), 2.34 (s, 4H), 1.95 (s, 3H), 1.87 (s, 2H).	547.25
N-(4-(4-氨基-7-(2-(4-甲基哌嗪-1-基)乙基)-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.19 (s, 1H), 7.73 (dt, J = 8.2, 3.4 Hz, 3H), 7.35 - 7.28 (m, 2H), 7.28 - 7.12 (m, 2H), 7.11 - 7.04 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 5.80 (t, J = 1.1 Hz, 1H), 5.53 (t, J = 1.4 Hz, 1H), 4.18 (t, J = 6.9 Hz, 2H), 2.47 (d, J = 7.0 Hz, 2H), 2.34 (s, 3H), 2.23 (s, 8H), 2.09 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	603.3

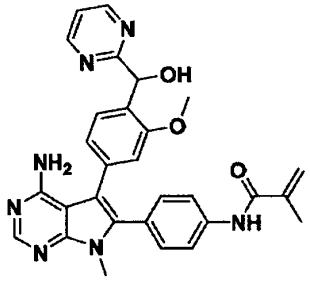
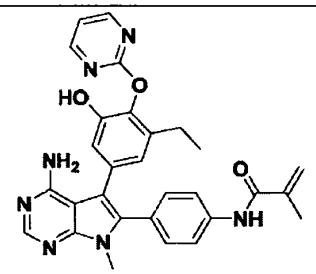
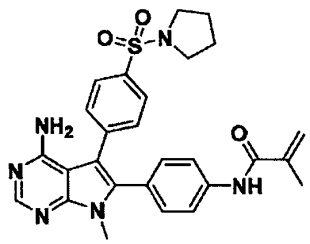
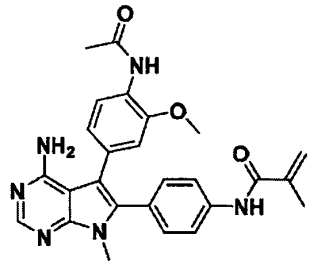
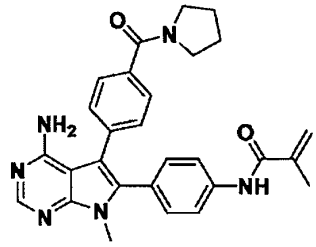
[0904]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-(2-羟乙基)-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.19 (s, 1H), 7.77 - 7.68 (m, 3H), 7.35 - 7.28 (m, 2H), 7.28 - 7.20 (m, 2H), 7.11 - 7.03 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 5.82 - 5.77 (m, 1H), 5.53 (t, J = 1.4 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.13 (t, J = 6.6 Hz, 2H), 3.58 (q, J = 6.4 Hz, 2H), 2.34 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	521.20
N-(4-(4-氨基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7-(2-N-吗啉基乙基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.19 (s, 1H), 7.73 (dt, J = 7.7, 3.5 Hz, 3H), 7.36 - 7.29 (m, 2H), 7.29 - 7.22 (m, 2H), 7.13 - 7.06 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.91 (s, 1H), 5.81 (s, 1H), 5.53 (s, 1H), 4.21 (t, J = 7.0 Hz, 2H), 3.44 (t, J = 4.6 Hz, 4H), 2.48 (d, J = 7.0 Hz, 2H), 2.34 (s, 3H), 2.22 (t, J = 4.7 Hz, 4H), 1.95 (s, 3H).	590.30
N-(4-(4-氨基-7-(2-(二甲基氨基)乙基)-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.73 (t, J = 7.6 Hz, 3H), 7.31 (d, J = 8.6 Hz, 2H), 7.28 - 7.20 (m, 2H), 7.12 - 7.05 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.90 (s, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 4.20 (t, J = 7.0 Hz, 2H), 2.38 (t, J = 7.1 Hz, 2H), 2.34 (s, 3H), 2.01 (s, 6H), 1.97 (s, 3H).	548.25
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 9.83 (s, 1H), 8.12 (s, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.65 - 7.58 (m, 2H), 7.42 - 7.34 (m, 2H), 7.34 - 7.26 (m, 2H), 7.23 - 7.15 (m, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.78 (s, 1H), 5.52 (t, J = 1.5 Hz, 1H), 2.38 (s, 3H), 1.94 (d, J = 1.3 Hz, 3H).	477.3

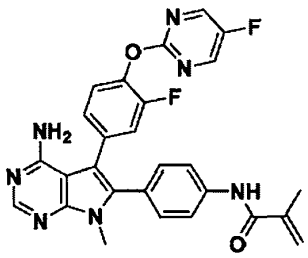
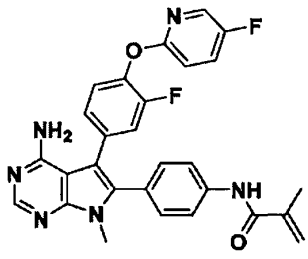
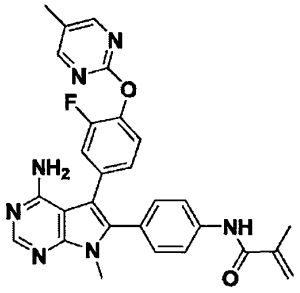
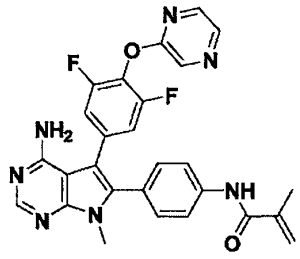
[0905]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((5-氯嘧啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.73 (s, 2H), 8.23 (s, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.44 - 7.31 (m, 2H), 7.20 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 1.9 Hz, 1H), 6.92 - 6.84 (m,1H), 6.59 - 6.31 (m, 1H), 6.30 - 6.26 (m, 1H), 6.06 (s, 2H), 5.85 - 5.73 (m, 1H), 3.60 (s, 3H), 3.55 (s, 3H).	528.20
N-(4-(4-氨基-5-(4-((5-氨基嘧啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (d, J = 14.0 Hz, 1H), 8.19 (d, J = 14.7 Hz, 1H), 7.93 (s, 2H), 7.81 - 7.58 (m, 2H), 7.48 - 7.20 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 6.88 - 6.80 (m, 1H), 6.50 - 6.40 (m, 1H), 6.35 - 6.22 (m, 1H), 5.78 (d, J = 10.1 Hz, 1H), 5.12 (s, 2H), 3.67 - 3.57 (m, 4H), 3.53 (s, 3H).	509.20
N-(4-(4-氨基-5-(3-甲氧基-4-(5-(甲基氨基)嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.21 (s, 1H), 7.93 (s, 2H), 7.73 (d, J = 8.6 Hz, 2H), 7.43 - 7.32 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.83 (dd, J = 8.1, 1.9 Hz, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.1 Hz, 1H), 5.96 (s, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 5.70 (q, J = 5.2 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 2.67 (d, J = 5.2 Hz, 3H).	523.35
N-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.71-8.72 (d, J = 4 Hz, 2H), 8.19 (s, 1H), 7.70-7.72 (d, J = 8 Hz, 2H), 7.30-7.34 (m, 3H), 7.03-7.05 (d, J = 8 Hz, 1H), 6.77-6.82 (m, 2H), 5.53-5.81 (m, 3H), 4.17 (s, 2H), 3.57-3.58 (m, 6H), 1.95 (s, 3H).	506.35

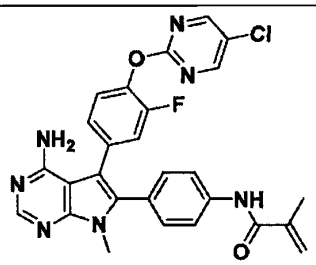
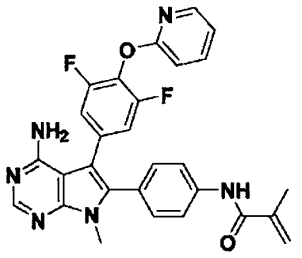
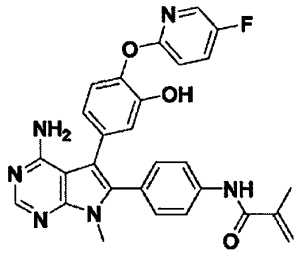
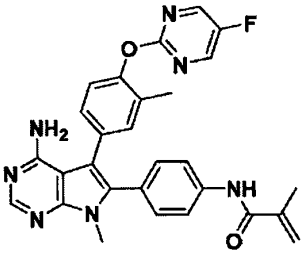
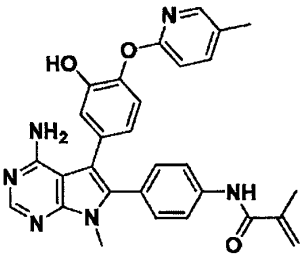
[0906]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-(羟基(邻甲苯基)甲基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.75-8.76 (d, J = 4 Hz, 2H), 8.19 (s, 1H), 7.70-7.72 (d, J = 8 Hz, 1H), 7.43-7.45 (d, J = 8 Hz, 1H), 7.30-7.37 (m, 3H), 6.78-6.87 (m, 1H), 6.77 (s, 1H), 5.99-6.01 (d, J = 8 Hz, 1H), 5.77-5.81 (m, 3H), 5.53 (s, 1H), 3.58 (s, 3H), 3.52 (s, 3H), 1.95 (s, 3H).	522.25
N-(4-(4-氨基-5-(3-乙基-5-羟基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.91 (d, J = 10.6 Hz, 1H), 9.54 (s, 1H), 8.64 (m, J = 19.1, 4.8 Hz, 2H), 8.17 (d, J = 17.0 Hz, 1H), 7.85 - 7.63 (m, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.20 (s, 1H), 6.92 - 6.48 (m, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 2.39 (q, J = 7.5 Hz, 2H), 1.96 (d, J = 3.4 Hz, 3H), 1.02 - 0.91 (m, 3H).	522.20
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-基磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.91 (s, 1H), 8.22 (s, 1H), 7.79 - 7.65 (m, 4H), 7.40 (d, J = 8.4 Hz, 2H), 7.25 - 7.17 (m, 2H), 6.03 (s, 2H), 5.79 (s, 1H), 5.54 (s, 1H), 3.63 (s, 3H), 3.21 - 3.00 (m, 4H), 1.95 (d, J = 1.6 Hz, 3H), 1.72 - 1.52 (m, 4H).	517.20
N-(4-(5-(4-乙酰胺基-3-甲氧基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.12 (s, 1H), 8.19 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.76 - 7.54 (m, 2H), 7.40 - 7.18 (m, 2H), 6.94 - 6.65 (m, 2H), 5.80 (t, J = 1.1 Hz, 1H), 5.59 - 5.35 (m, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 2.08 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	471.15
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.77 - 7.66 (m, 2H), 7.55 - 7.43 (m, 2H), 7.33 - 7.20 (m, 4H), 5.92 (s, 1H), 5.83 - 5.77 (m, 1H), 5.53 (q, J = 1.4 Hz, 1H), 3.61 (s, 3H), 3.44 (dt, J = 16.1, 6.5 Hz, 4H), 1.95 (t, J = 1.3 Hz, 3H), 1.83 (dq, J = 18.0, 6.6 Hz, 4H).	481.35

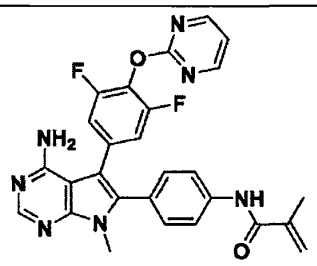
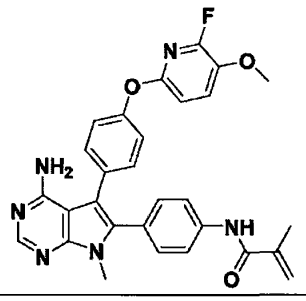
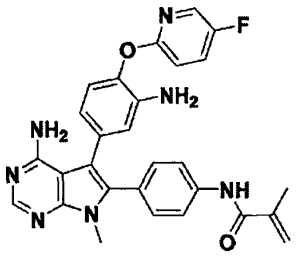
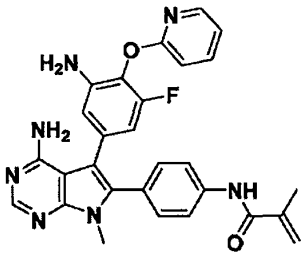
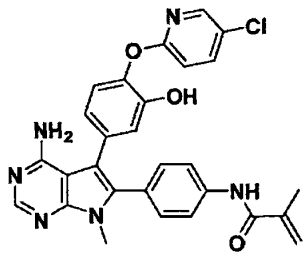
[0907]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((5-氟嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.78 (s, 2H), 8.22 (s, 1H), 7.85 - 7.71 (m, 2H), 7.42 - 7.29 (m, 3H), 7.21 (dd, J = 11.6, 2.0 Hz, 1H), 7.12 (dd, J = 8.4, 2.0 Hz, 1H), 6.00 (s, 1H), 5.81 (s, 1H), 5.55 (s, 1H), 3.59 (s, 3H), 1.96 (d, J = 1.6 Hz, 2H).	514.35
N-(4-(4-氨基-5-(3-氟-4-((5-氟吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.94 (s, 1H), 8.29 (s, 1H), 8.17 (d, J = 3.1 Hz, 1H), 7.86 (ddd, J = 9.0, 7.9, 3.1 Hz, 1H), 7.80 - 7.73 (m, 2H), 7.34 (s, 1H), 7.36 - 7.26 (m, 2H), 7.25 - 7.16 (m, 2H), 7.13 - 7.06 (m, 1H), 6.37 (s, 2H), 5.82 (s, 1H), 5.55 (d, J = 2.0 Hz, 1H), 3.62 (s, 3H), 1.96 (d, J = 1.2 Hz, 3H).	513.20
N-(4-(4-氨基-5-(3-氟-4-((5-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.42 (d, J = 5.6 Hz, 2H), 8.21 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 6.91 - 6.86 (m, 2H), 6.86 - 6.80 (m, 1H), 6.50 - 6.39 (m, 1H), 6.33 - 6.23 (m, 1H), 6.14 (s, 2H), 5.82 - 5.75 (m, 1H), 3.65 - 3.54 (d, J = 23.2 Hz, 6H).	510.20
N-(4-(4-氨基-5-(3,5-二氟-4-(吡嗪-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.77 (d, J = 1.4 Hz, 1H), 8.48 (d, J = 2.7 Hz, 1H), 8.27 (dd, J = 2.7, 1.5 Hz, 1H), 8.22 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.16 (s, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 3.58 (s, 3H), 1.96 (s, 3H).	514.20

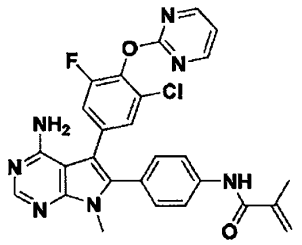
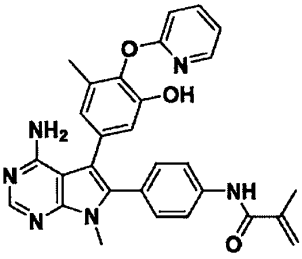
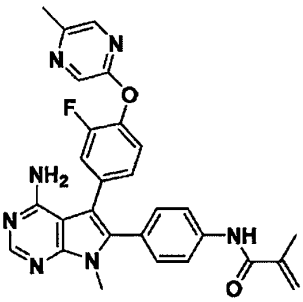
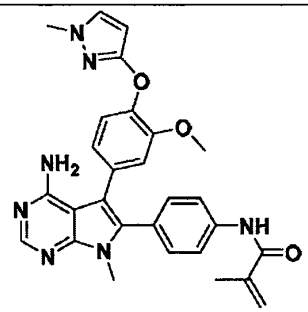
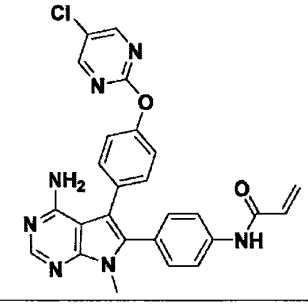
[0908]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((5-氯嘧啶-2-基)氧基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.81 (s, 2H), 8.22 (s, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.47 - 7.30 (m, 3H), 7.23 - 7.06 (m, 2H), 5.81 (s, 1H), 5.55 (s, 1H), 3.59 (s, 3H), 1.96 (s, 3H).	530.15
N-(4-(4-氨基-5-(3,5-二氟-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.22 (s, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.92 (td, J = 8.4, 7.8, 2.2 Hz, 1H), 7.78 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.25 - 7.15 (m, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.13 (s, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 3.58 (s, 3H), 1.96 (s, 3H).	513.35
N-(4-(4-氨基-5-(4-((5-氟吡啶-2-基)氧基)-3-羟基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.61 (s, 1H), 8.23 - 8.10 (m, 2H), 7.81 - 7.71 (m, 3H), 7.31 (d, J = 8.4 Hz, 2H), 7.09 - 6.96 (m, 2H), 6.81 (d, J = 2.2 Hz, 1H), 6.70 (dd, J = 8.0, 2.2 Hz, 1H), 5.81 (s, 1H), 5.54 (s, 1H), 3.60 (s, 3H), 1.96 (s, 3H).	511.20
N-(4-(4-氨基-5-(4-((5-氟嘧啶-2-基)氧基)-3-甲基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.91 (s, 1H), 8.74 (s, 2H), 8.20 (s, 1H), 7.77 - 7.71 (m, 2H), 7.37 - 7.30 (m, 2H), 7.25 (s, 1H), 7.11 (d, J = 1.3 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 2.06 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	509.20
N-(4-(4-氨基-5-(3-羟基-4-((5-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.90 (d, J = 3.1 Hz, 1H), 9.51 (d, J = 6.1 Hz, 1H), 8.17 (d, J = 14.7 Hz, 1H), 7.98 (s, 0H), 7.73 (dd, J = 8.6, 6.1 Hz, 2H), 7.65 - 7.56 (m, 1H), 7.30 (dd, J = 13.8, 8.6 Hz, 2H), 6.94 - 6.76 (m, 4H), 5.82 (s, 1H), 5.55 (s, 1H), 3.60 (d, J = 4.6 Hz, 3H), 2.22 (s, 3H), 1.97 (dd, J = 3.1, 1.8 Hz, 3H).	507.20

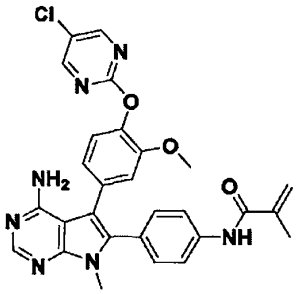
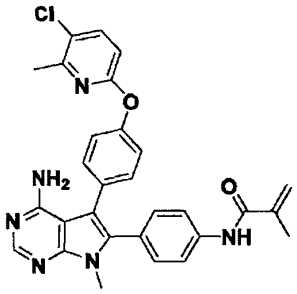
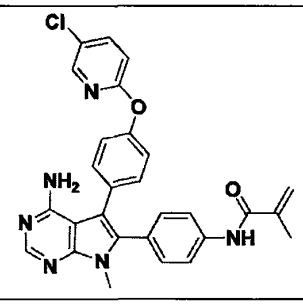
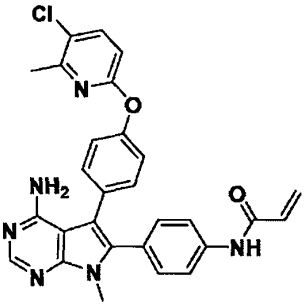
[0909]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3,5-二氟-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.95 (s, 1H), 8.72 (d, J = 4.8 Hz, 2H), 8.22 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.42 - 7.33 (m, 3H), 7.08 (d, J = 8.8 Hz, 2H), 6.13 (s, 2H), 5.82 (s, 1H), 5.55 (s, 1H), 3.57 (s, 3H), 1.96 (s, 3H).	514.35
N-(4-(4-氨基-5-(4-((6-氟-5-甲氧基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.86 - 7.65 (m, 3H), 7.28 (m, *J* = 12.2, 8.3 Hz, 4H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.99 - 6.71 (m, 1H), 5.80 (s, 2H), 5.53 (s, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 1.95 (s, 3H).	525.15
N-(4-(4-氨基-5-(3-氨基-4-((5-氟吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.20 - 8.13 (m, 2H), 7.83 - 7.73 (m, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.02 (dd, J = 9.1, 3.6 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 2.1 Hz, 1H), 6.41 (dd, J = 8.1, 2.1 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 5.01 (s, 2H), 3.60 (s, 3H), 2.08 (s, 1H), 1.96 (s, 3H).	510.20
N-(4-(4-氨基-5-(3-氨基-5-氟-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.25 - 8.07 (m, 2H), 7.91 - 7.70 (m, 3H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.17 - 6.99 (m, 2H), 6.53 (s, 1H), 6.24 (dd, *J* = 10.8, 2.0 Hz, 1H), 5.82 (s, 1H), 5.54 (s, 1H), 5.34 (s, 2H), 3.59 (s, 3H), 1.96 (s, 3H).	510.20
N-(4-(4-氨基-5-(4-((5-氯吡啶-2-基)氧基)-3-羟基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.91 (d, J = 4.6 Hz, 1H), 9.65 (d, J = 5.8 Hz, 1H), 8.25 - 8.10 (m, 2H), 7.92 - 7.85 (m, 1H), 7.73 (dd, J = 8.6, 6.5 Hz, 2H), 7.30 (dd, J = 11.6, 8.6 Hz, 2H), 7.07 - 6.92 (m, 2H), 6.92 - 6.77 (m, 2H), 6.20 (s, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 3.60 (d, J = 1.5 Hz, 3H), 1.97 (d, J = 3.3 Hz, 3H).	527.30

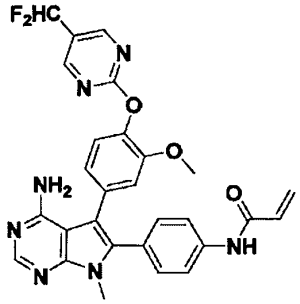
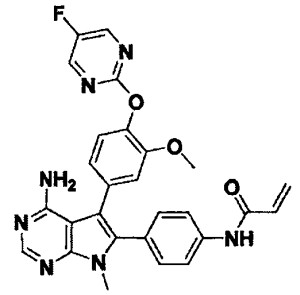
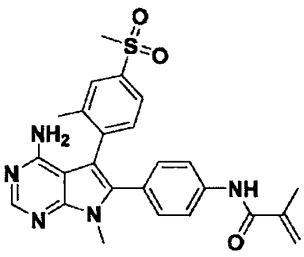
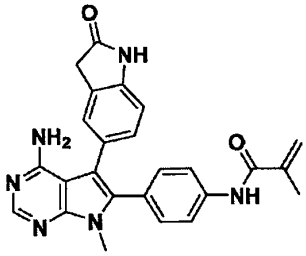
[0910]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氯-5-氟-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.96 (s, 1H), 8.71 (d, J = 4.8 Hz, 2H), 8.22 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.40 - 7.34 (m, 3H), 7.28 - 7.17 (m, 2H), 5.83 (s, 1H), 5.55 (s, 1H), 3.57 (s, 3H), 1.96 (s, 3H).	530.15
N-(4-(4-氨基-5-(3-羟基-5-甲基-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.42 (s, 1H), 8.21 - 8.06 (m, 2H), 7.76 (p, J = 11.6, 9.8 Hz, 3H), 7.32 (dd, J = 16.8, 8.4 Hz, 2H), 7.11 - 6.88 (m, 2H), 6.71 (dd, J = 49.6, 10.1 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.59 (d, J = 5.8 Hz, 3H), 2.15 - 1.89 (m, 6H).	507.30
N-(4-(4-氨基-5-(3-氟-4-((5-甲基吡嗪-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.50 (d, J = 1.3 Hz, 1H), 8.21 (s, 1H), 8.11 (s, 1H), 7.75 (d, J = 8.6 Hz, 2H), 7.33 (dd, J = 8.5, 3.7 Hz, 3H), 7.19 (dd, J = 11.6, 2.0 Hz, 1H), 7.10 (d, J = 9.2 Hz, 1H), 6.02 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 2.45 (s, 3H), 1.96 (s, 3H).	510.20
N-(4-(4-氨基-5-(3-甲氧基-4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.19 (s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 2.3 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.79 - 6.71 (m, 1H), 5.81 (s, 1H), 5.70 (d, J = 2.3 Hz, 1H), 5.54 (s, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.60 (s, 3H), 2.00 - 1.89 (m, 3H).	510.45
N-(4-(4-氨基-5-(4-((5-氯嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.78 (s, 2H), 8.21 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.37 - 7.26 (m, 4H), 7.27 - 7.21 (m, 2H), 6.45 (dd, J = 17.2, 10.0 Hz, 1H), 6.28 (dd, J = 17.2, 2.0 Hz, 1H), 5.78 (dd, J = 10.0, 2.0 Hz, 2H), 3.60 (s, 3H).	498.10

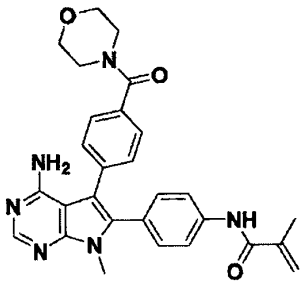
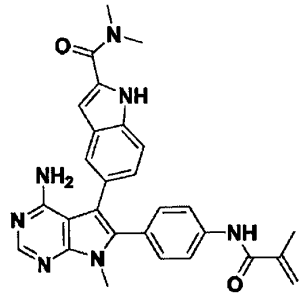
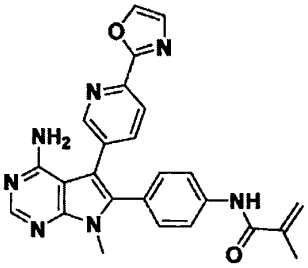
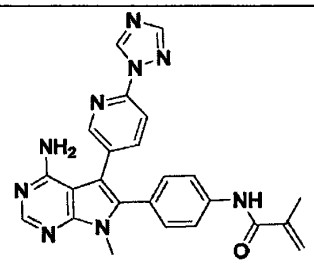
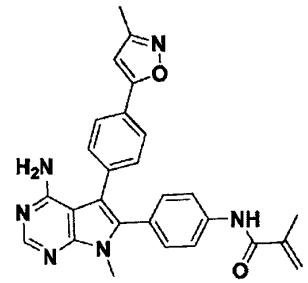
[0911]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((5-氯嘧啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.74 (s, 2H), 8.21 (s, 1H), 7.78 - 7.72 (m, 2H), 7.39 - 7.32 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 1.9 Hz, 1H), 6.87 (dd, J = 8.1, 1.9 Hz, 1H), 5.98 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.58 (d, J = 14.3 Hz, 6H), 1.96 (s, 3H).	542.15
N-(4-(4-氨基-5-(4-((5-氯-6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.28 (t, J = 8.4 Hz, 4H), 7.16 - 7.08 (m, 2H), 6.89 (d, J = 8.7 Hz, 1H), 5.94 (s, 3H), 5.80 (s, 1H), 5.54 (s, 1H), 3.62 (s, 3H), 2.40 (s, 3H), 1.95 (s, 3H).	525.20
N-(4-(4-氨基-5-(4-((5-氯吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.34 - 8.09 (m, 2H), 8.09 - 7.89 (m, 1H), 7.78 - 7.57 (m, 2H), 7.35 - 7.20 (m, 4H), 7.21 - 7.04 (m, 3H), 5.80 (d, J = 1.3 Hz, 3H), 5.54 (t, J = 1.4 Hz, 1H), 3.60 (d, J = 5.2 Hz, 3H), 1.95 (d, J = 1.2 Hz, 3H).	511.15
N-(4-(4-氨基-5-(4-((5-氯-6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.20 (s, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.73 - 7.67 (m, 2H), 7.34 - 7.23 (m, 4H), 7.15 - 7.08 (m, 2H), 6.89 (d, J = 8.6 Hz, 1H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 16.9, 2.0 Hz, 1H), 5.96 (s, 2H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.62 (s, 3H), 2.40 (s, 3H).	511.20

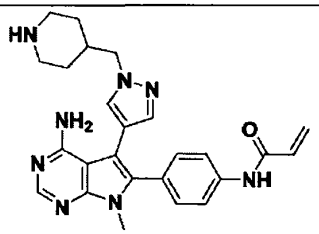
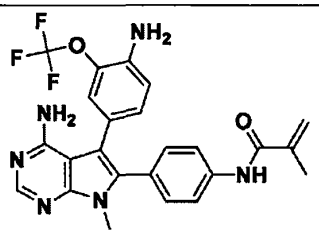
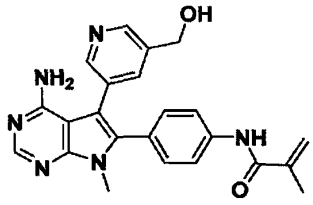
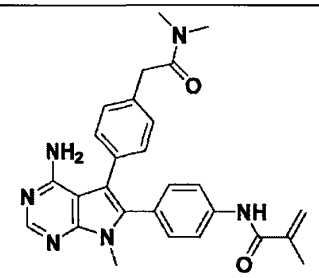
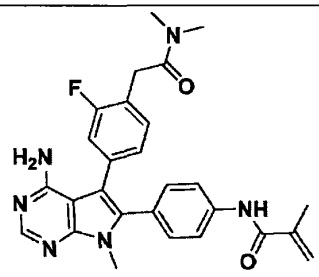
[0912]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((5-(二氟甲基)嘧啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.87 (s, 2H), 8.22 (s, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.15 (s, 0H), 7.03 - 6.98 (m, 1H), 6.89 (dd, J = 8.0, 1.9 Hz, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 16.9, 2.0 Hz, 1H), 6.00 (s, 2H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H).	544.2
N-(4-(4-氨基-5-(4-((5-氟嘧啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.71 (s, 2H), 8.21 (s, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.40 - 7.34 (m, 2H), 7.18 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 6.87 (dd, J = 8.0, 2.0 Hz, 1H), 6.45 (dd, J = 17.0, 10.2 Hz, 1H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 5.99 (s, 1H), 5.79 (dd, J = 10.2, 2.0 Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H).	512.30
N-(4-(4-氨基-7-甲基-5-(2-甲基-4-(甲基磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.21 (s, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.75 - 7.63 (m, 3H), 7.45 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 5.78 (s, 1H), 5.72 (s, 2H), 5.52 (s, 1H), 3.66 (s, 3H), 3.30 (s, 1H), 3.23 (s, 3H), 2.08 (s, 3H), 1.93 (s, 3H).	476.30
N-(4-(4-氨基-7-甲基-5-(2-侧氧基吲哚啉-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.88 (s, 1H), 8.17 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.10 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 5.79 (s, 1H), 5.53 (s, 1H), 3.59 (s, 3H), 3.44 (s, 2H), 1.95 (s, 3H).	439.3

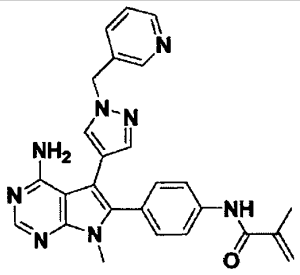
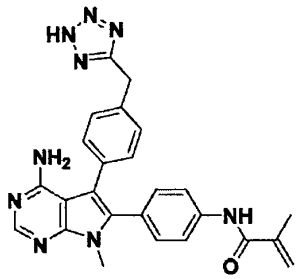
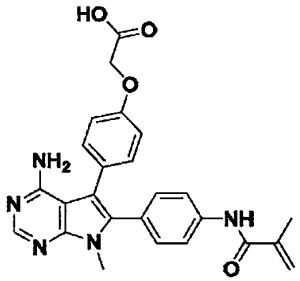
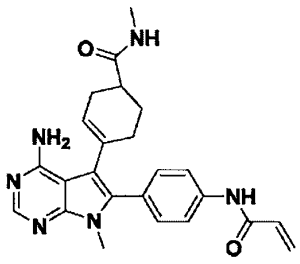
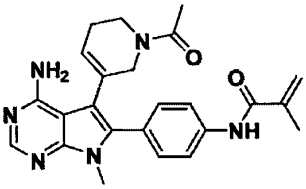
[0913]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吗啉-4-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.41 - 7.34 (m, 2H), 7.30 - 7.22 (m, 4H), 5.98 (s, 1H), 5.80 (s, 1H), 5.54 (d, J = 1.7 Hz, 1H), 3.32 (s, 11H), 1.95 (t, J = 1.2 Hz, 3H).	497.20
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N,N-二甲基-1H-吲哚-2-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 9.83 (s, 1H), 8.18 (s, 1H), 7.68 - 7.61 (m, 2H), 7.50 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.07 (dd, J = 8.4, 1.6 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 5.77 (s, 1H), 5.51 (d, J = 1.9 Hz, 1H), 3.63 (s, 3H), 3.11 (s, 6H), 1.93 (t, J = 1.2 Hz, 3H).	494.30
N-(4-(4-氨基-7-甲基-5-(6-(恶唑-2-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.41 (d, J = 2.2 Hz, 1H), 8.28 (s, 1H), 8.23 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.80 - 7.70 (m, 3H), 7.45 (s, 1H), 7.33 - 7.25 (m, 2H), 6.15 (s, 2H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.62 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	452.1
N-(4-(5-(6-(1H-1,2,4-三唑-1-基)吡啶-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.37 (s, 1H), 8.32 - 8.25 (m, 2H), 8.23 (s, 1H), 7.85 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.17 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.62 (s, 3H), 1.95 (s, 3H).	452.30
N-(4-(4-氨基-7-甲基-5-(4-(3-甲基异恶唑-5-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.79 (d, J = 7.9 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.85 (s, 1H), 5.97 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 2.50 (s, 3H), 1.94 (s, 3H).	465.30

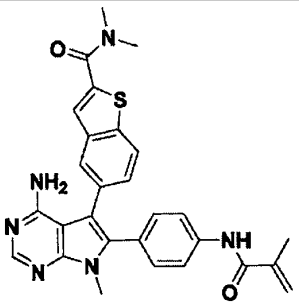
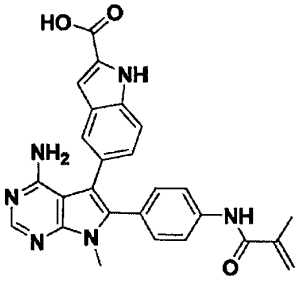
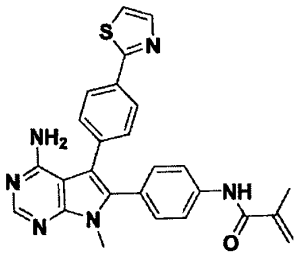
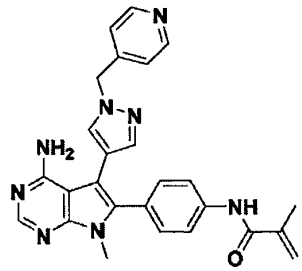
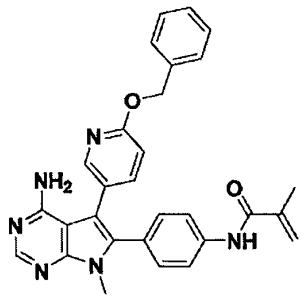
[0914]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-(哌啶-4-基甲基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.36 (s, 1H), 7.85 - 7.70 (m, 2H), 7.59 - 7.50 (m, 2H), 7.41 - 7.33 (m, 2H), 6.48 (dd, J = 17.0, 9.4 Hz, 2H), 8.85 (dd, J = 17.0, 2.5 Hz, 1H), 4.10 (dd, J = 9.4, 2.5 Hz, 2H), 3.80 (d, J = 7.1 Hz, 3H), 3.41 (s, 2H), 3.01 (d, J = 12.7 Hz, 2H), 2.20 - 2.01 (m, 1H), 1.81 - 1.61 (d, J = 14.0 Hz, 2H), 1.55 - 1.23 (m, 2H).	457.3
N-(4-(4-氨基-5-(4-氨基-3-(三氟甲氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.17 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 6.95-6.89 (m, 2H), 6.78 (d, J = 8.7 Hz, 1H), 5.90 (s, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 5.44 (s, 2H), 3.58 (s, 3H), 1.96 (s, 3H).	483.15
N-(4-(4-氨基-5-(5-(羟基甲基)吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.40 (d, J = 2.0 Hz, 1H), 8.24 - 8.17 (m, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 2.5 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 5.32 (t, J = 5.6 Hz, 1H), 4.53 (d, J = 5.6 Hz, 2H), 3.61 (s, 3H), 3.30 (s, 1H), 1.95 (s, 3H).	415.2
N-(4-(4-氨基-5-(4-(2-(二甲基氨基)-2-侧氧基乙基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.19 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.17-7.22 (m, 4H), 5.80 (s, 1H), 5.53 (s, 1H), 3.69 (s, 2H), 3.60 (s, 3H), 3.01 (s, 3H), 2.84 (s, 3H), 1.95 (s, 3H).	469.20
N-(4-(4-氨基-5-(4-(2-(二甲基氨基)-2-侧氧基乙基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.75 - 7.69 (m, 2H), 7.33 - 7.26 (m, 2H), 7.22 (t, J = 7.9 Hz, 1H), 7.02 (dd, J = 7.7, 1.7 Hz, 1H), 6.97 (dd, J = 10.9, 1.7 Hz, 1H), 5.91 -5.81 (s, 2H), 5.54 (d, J = 2.0 Hz, 1H), 3.70 (s, 2H), 3.59 (s, 3H), 3.05 (s, 3H), 2.85 (s, 3H), 1.95 (s, 3H).	487.20

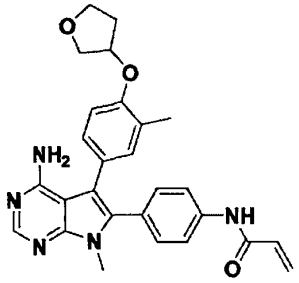
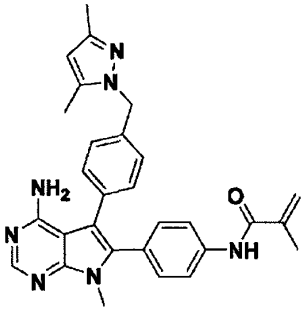
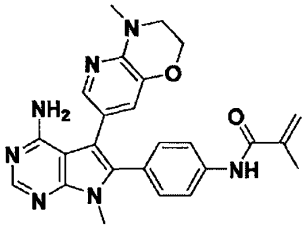
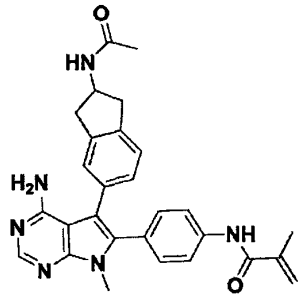
[0915]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-(吡啶-3-基甲基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.52 - 8.43 (m, 2H), 8.16 (s, 1H), 7.84 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.49 - 7.42 (m, 1H), 7.40 - 7.29 (m, 4H), 5.81 (s, 1H), 5.55 (s, 1H), 5.37 (s, 2H), 3.59 (s, 2H), 1.97 (s, 3H).	465.4
N-(4-(5-(4-((2H-四唑-5-基)甲基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.20 (s, 1H), 7.68 - 7.62 (m, 2H), 7.27 (d, J = 8.1 Hz, 6H), 5.82 (s, 1H), 5.54 (s, 1H), 4.27 (s, 2H), 3.70 (s, 3H), 2.04 (t, J = 1.2 Hz, 3H), 1.33 (d, J = 15.8 Hz, 1H).	466.20
2-(4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯氧基)乙酸		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 9.88 (s, 1H), 8.18 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.28 (dd, J = 12.5, 8.1 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 4.65 (s, 2H), 3.60 (s, 3H), 1.95 (s, 3H).	458.40
4-(6-(4-乙酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.10 (s, 1H), 7.78 (dd, J = 7.8, 5.9 Hz, 3H), 7.44 (d, J = 8.5 Hz, 2H), 6.48 (dd, J = 17.0, 10.1 Hz, 2H), 6.30 (dd, J = 17.0, 2.1 Hz, 1H), 5.83 - 5.74 (m, 2H), 3.57 (s, 3H), 2.57 (d, J = 4.5 Hz, 3H), 2.45 (q, J = 6.2 Hz, 3H), 2.29 (s, 1H), 2.24 (s, 2H), 1.89 (s, 2H), 1.65 (d, J = 6.2 Hz, 2H).	431.25
N-(4-(5-(1-乙酰基-1,2,5,6-四氢吡啶-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (d, J = 6.3 Hz, 1H), 8.15 (d, J = 5.0 Hz, 1H), 7.82 (t, J = 8.2 Hz, 2H), 7.44 (dd, J = 10.6, 8.4 Hz, 2H), 6.35 (s, 2H), 6.05 - 5.81 (m, 2H), 5.56 (s, 1H), 3.78 (d, J = 34.2 Hz, 2H), 3.55 (t, J = 5.9 Hz, 4H), 3.48 (t, J = 5.7 Hz, 1H), 2.23 (d, J = 27.7 Hz, 2H), 1.99 (d, J = 11.9 Hz, 4H), 1.55 (s, 2H).	431.25

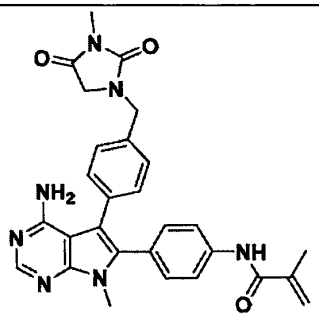
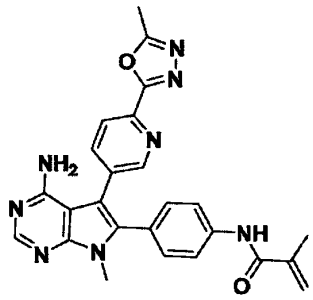
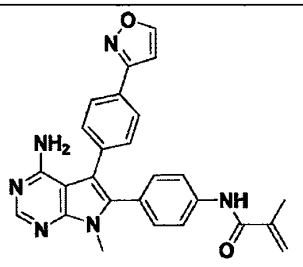
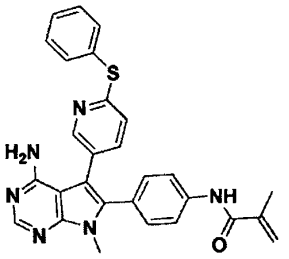
[0916]

化合物	结构	质子 NMR	MS [M+1]
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N,N-二甲基苯并[b]噻吩-2-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.21 (s, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.84 - 7.77 (m, 2H), 7.71 - 7.64 (m, 2H), 7.32 - 7.23 (m, 3H), 5.78 (s, 1H), 5.52 (d, J = 1.9 Hz, 1H), 3.63 (s, 3H), 3.20 (s, 3H), 3.07 (s, 3H), 1.93 (s, 3H).	511.2
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-1H-吲哚-2-甲酸		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.45 - 12.25 (s, 1H), 11.85 (s, 1H), 9.85 (d, J = 12.7 Hz, 1H), 8.25 (d, J = 12.7 Hz, 1H),7.78 - 7.65 (m, 2H), 7.54 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.35 - 7.20 (m, 2H), 7.20 - 7.01 (dd, J = 8.5, 1.7 Hz, 2H), 6.20 - 5.60 (d, J = 2.1 Hz, 2H), 5.60 - 5.40 (s, 1H), 3.65 (t, J = 1.5 Hz,3H), 1.95 (d, J = 1.4 Hz, 3H).	467.25
N-(4-(4-氨基-7-甲基-5-(4-(噻唑-2-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.95 - 7.89 (m, 3H), 7.79 (d, J = 3.2 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.31 (dd, J = 18.0, 8.0 Hz, 4H), 5.79 (s, 2H), 5.53 (s, 1H), 3.62 (s, 3H), 1.94 (s, 3H), 1.18 (d, J = 13.5 Hz, 1H).	467.20
N-(4-(4-氨基-7-甲基-5-(1-(吡啶-4-基甲基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.54 - 8.48 (m, 2H), 8.17 (s, 1H), 7.83 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 5.4 Hz, 2H), 5.81 (s, 1H), 5.56 (s, 1H), 5.40 (s, 2H), 3.61 (s, 3H), 1.97 (s, 3H).	465.2
N-(4-(4-氨基-5-(6-(苯甲氧基)吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.20 (s, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.76 - 7.68 (m, 2H), 7.57 (dd, J = 8.5, 2.4 Hz, 1H), 7.49 - 7.25 (m, 7H), 6.87 (d, J = 8.5 Hz, 1H), 5.94 (s, 1H), 5.81 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 5.31 (s, 2H), 3.60 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	491.30

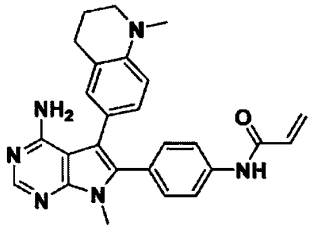
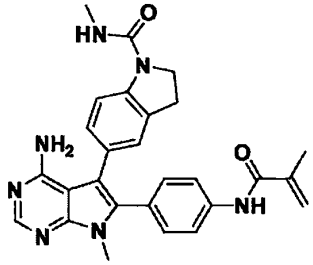
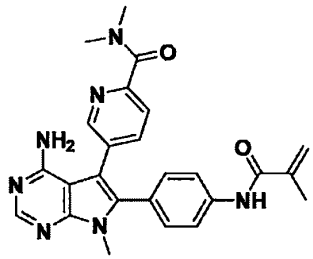
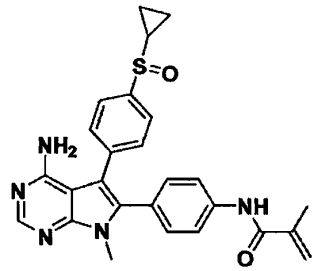
[0917]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(3-甲基-4-(四氢呋喃-3-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.17 (d, J = 2.2 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.33 - 7.22 (m, 2H), 7.09 - 6.96 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.44 (dd, J = 16.9, 10.1 Hz, 1H), 6.27 (dd, J = 16.9, 2.1 Hz, 1H), 5.81 - 5.74 (m, 1H), 5.01 (d, J = 5.6 Hz, 1H), 3.94 - 3.72 (m, 4H), 3.59 (d, J = 5.5 Hz, 3H), 2.19 (dt, J = 14.5, 7.0 Hz, 1H), 2.09 (s, 3H), 1.99 (d, J = 14.4 Hz, 1H).	470.30
N-(4-(4-氨基-5-(4-((3,5-二甲基-1H-吡唑-1-基)甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.18 (s, 1H), 7.73 - 7.65 (m, 2H), 7.29 - 7.18 (m, 4H), 7.05 (d, J = 8.0 Hz, 2H), 5.99 - 5.75 (s, 3H), 5.55 (m, 1H), 5.20 (m, 2H), 3.65 (s, 3H), 2.15 (s, 3H), 2.10 (d, J = 0.7 Hz, 3H), 1.95 (s, 3H).	492.3
N-(4-(4-氨基-7-甲基-5-(4-甲基-3,4-二氢-2H-吡啶并[3,2-b][1,4]恶嗪-7-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.17 (s, 1H), 7.76 - 7.68 (m, 2H), 7.50 (d, J = 1.9 Hz, 1H), 7.33 - 7.26 (m, 2H), 6.78 (d, J = 2.0 Hz, 1H), 5.91 (s, 2H), 5.81 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 4.20 (t, J = 4.5 Hz, 2H), 3.57 (s, 3H), 3.43 (t, J = 4.5 Hz, 2H), 3.01 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	456.35
N-(4-(5-(2-乙酰胺基-2,3-二氢-1H-茚-5-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 - 8.12 (m, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 7.12 (s, 1H), 7.02 (d, J = 7.8 Hz, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 4.45 (q, J = 6.8 Hz, 1H), 3.59 (s, 3H), 3.14 (td, J = 15.7, 7.6 Hz, 2H), 2.72 (td, J = 15.1, 5.8 Hz, 2H), 1.95 (s, 3H), 1.79 (s, 3H).	481.30

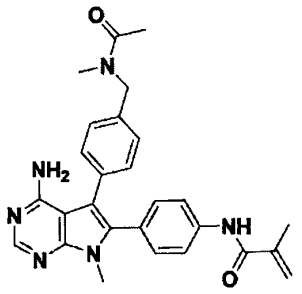
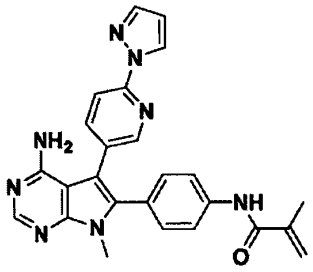
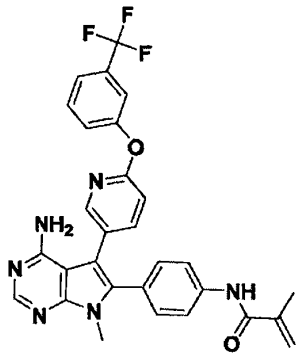
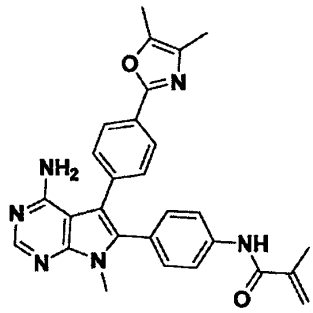
[0918]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((3-甲基-2,4-二侧氧基咪唑啶-1-基)甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.19 (s, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.30 - 7.19 (m, 6H), 5.80 (s, 1H), 5.53 (s, 1H), 4.50 (s, 2H), 3.91 (s, 2H), 3.60 (s, 3H), 2.88 (s, 3H), 1.95 (s, 3H).	510.2
N-(4-(4-氨基-7-甲基-5-(6-(5-甲基-1,3,4-恶二唑-2-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.43 (d, J = 2.2 Hz, 1H), 8.24 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.81 (dd, J = 8.1, 2.2 Hz, 1H), 7.77 - 7.70 (m, 2H), 7.32 - 7.25 (m, 2H), 6.20 (s, 2H), 5.80 (s, 1H), 5.54 (d, J = 1.7 Hz, 1H), 3.62 (s, 3H), 2.60 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H).	467.35
N-(4-(4-氨基-5-(4-(异恶唑-3-基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.00 (d, J = 1.8 Hz, 1H), 8.22 (s, 1H), 7.90 - 7.84 (m, 2H), 7.75 - 7.68 (m, 2H), 7.39 - 7.32 (m, 2H), 7.32 - 7.25 (m, 2H), 7.15 (d, J = 1.7 Hz, 1H), 6.15 - 5.75 (s, 3H), 5.55 - 5.50 (m, 1H), 3.62 (s, 3H), 1.95 (s, 3H).	451.2
N-(4-(4-氨基-7-甲基-5-(6-(苯硫基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 - 8.14 (m, 2H), 7.76 - 7.70 (m, 2H), 7.64 - 7.57 (m, 2H), 7.49 (dt, J = 7.2, 2.1 Hz, 4H), 7.30 - 7.23 (m, 2H), 6.92 (d, J = 8.3 Hz, 1H), 6.02 (s, 2H), 5.81 (s, 1H), 5.55 (s, 1H), 3.58 (s, 2H), 1.96 (d, J = 1.4 Hz, 3H).	493.30

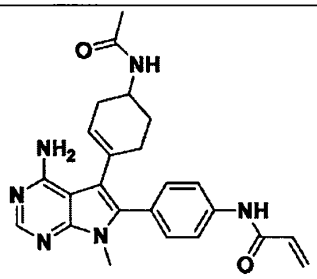
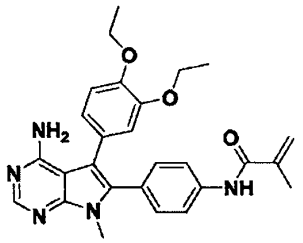
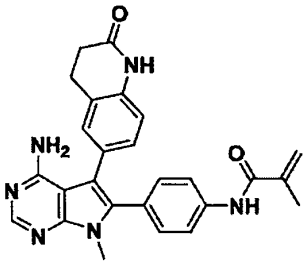
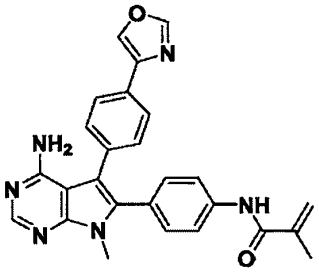
[0919]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-甲基-1,2,3,4-四氢喹啉-6-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.15 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.86 (dd, J = 8.2, 2.1 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.1, 2.1 Hz, 1H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.58 (s, 3H), 3.19 (t, J = 5.6 Hz, 2H), 2.82 (s, 3H), 2.63 (t, J = 6.5 Hz, 2H), 1.87 (p, J = 6.1 Hz, 2H).	439.30
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基吲哚啉-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.17 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.31 - 7.24 (m, 2H), 7.01 (d, J = 1.7 Hz, 1H), 6.95 (dd, J = 8.2, 1.9 Hz, 1H), 6.57 (q, J = 4.4 Hz, 1H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.86 (t, J = 8.7 Hz, 2H), 3.60 (s, 3H), 3.07 (t, J = 8.7 Hz, 2H), 2.66 (d, J = 4.3 Hz, 3H), 1.95 (t, J = 1.2 Hz, 3H).	482.30
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N,N-二甲基吡啶酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.30 (s, 1H), 8.23 (s, 1H), 7.72 (t, J = 9.9 Hz, 3H), 7.51 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 6.16 - 6.10 (m, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.62 (s, 3H), 2.99 (d, J = 4.8 Hz, 6H), 1.95 (s, 3H).	456.25
N-(4-(4-氨基-5-(4-(环丙基亚磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.68 - 7.62 (m, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.31 - 7.24 (m, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 2.43 (s, 1H), 1.95 (s, 3H), 1.07 - 0.81 (m, 4H).	472.1

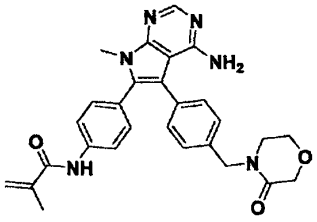
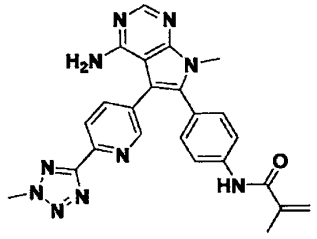
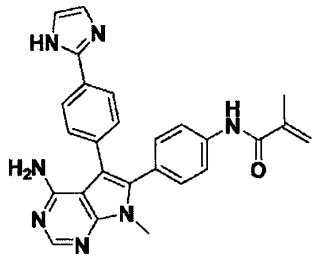
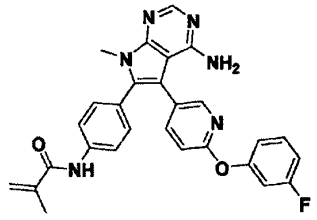
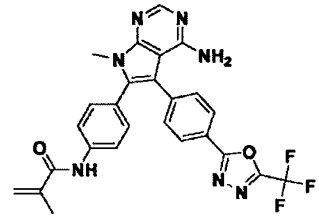
[0920]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((N-甲基乙酰胺基)甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.20 (d, J = 2.8 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 7.9 Hz, 1H), 7.31 - 7.22 (m, 5H), 5.81 (s, 1H), 5.54 (s, 1H), 4.63 (d, J = 15.5 Hz, 2H), 3.70 (d, J = 1.7 Hz, 3H), 3.04 (s, 2H), 2.94 (s, 1H), 2.18 (d, J = 6.6 Hz, 3H), 2.04 (s, 3H).	469.35
N-(4-(5-(6-(1H-吡唑-1-基)吡啶-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.60 (d, J = 2.6 Hz, 1H), 8.24 - 8.18 (m, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.85 - 7.75 (m, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.57 (t, J = 2.2 Hz, 1H), 6.12 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.62 (s, 3H), 1.94 (s, 3H).	451.1
N-(4-(4-氨基-7-甲基-5-(6-(3-(三氟甲基)苯氧基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.20 (s, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.74 (s, 1H), 7.74 - 7.65 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.60 - 7.54 (m, 2H), 7.51 (d, J = 8.3 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.10 (d, J = 8.4 Hz, 1H), 6.08 (s, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.32 (s, 3H), 1.95 (s, 3H).	545.25
N-(4-(4-氨基-5-(4-(4,5-二甲基恶唑-2-基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.87 - 7.80 (m, 2H), 7.74 - 7.67 (m, 2H), 7.35 - 7.28 (m, 2H), 7.31 - 7.23 (m, 2H), 5.94 (s, 2H), 5.82 - 5.77 (m, 1H), 5.55 - 5.50 (m, 1H), 3.62 (s, 3H), 2.31 (d, J = 1.2 Hz, 3H), 2.09 (d, J = 1.1 Hz, 3H), 1.95 (t, J = 1.2 Hz, 3H).	479.35

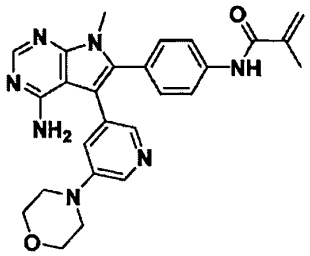
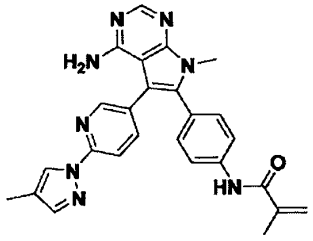
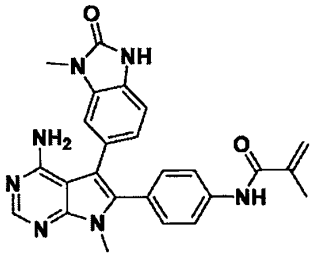
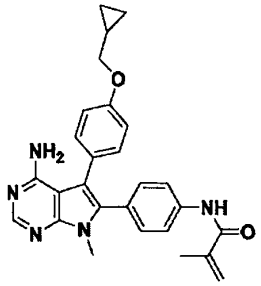
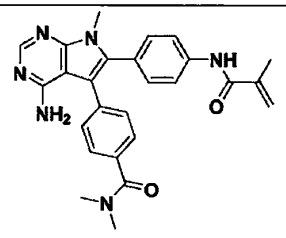
[0921]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-(4-乙酰胺基环己-1-烯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.12 (s, 1H), 7.85 - 7.76 (m, 2H), 7.74 (d, J = 7.3 Hz, 1H), 7.49 - 7.41 (m, 2H), 6.47 (dd, J = 17.0, 10.1 Hz, 1H), 6.36 - 6.21 (m, 3H), 5.80 (dd, J = 10.1, 2.1 Hz, 1H), 5.69 (d, J = 4.1 Hz, 1H), 3.80 (s, 1H), 3.57 (s, 3H), 2.34 (d, J = 16.4 Hz, 1H), 2.10 - 1.88 (m, 3H), 1.80 (s, 3H), 1.66 (d, J = 12.7 Hz, 1H), 1.46 (s, 1H).	431.15
N-(4-(4-氨基-5-(3,4-二乙氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.2 Hz, 1H), 6.79 - 6.70 (m, 2H), 6.13 (s, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.87 (q, J = 7.0 Hz, 2H), 3.33 (s, 3H), 1.95 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H).	472.30
N-(4-(4-氨基-7-甲基-5-(2-侧氧基-1,2,3,4-四氢喹啉-6-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.89 (s, 1H), 8.17 (s, 1H), 7.73 - 7.67 (m, 2H), 7.32 - 7.25 (m, 2H), 7.09 (d, J = 1.9 Hz, 1H), 6.98 (dd, J = 8.0, 2.0 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 5.80 (s, 2H), 5.54 (d, J = 1.9 Hz, 1H), 3.59 (s, 3H), 2.83 (t, J = 7.5 Hz, 2H), 2.44 (dd, J = 8.5, 6.5 Hz, 2H), 1.95 (d, J = 1.3 Hz, 3H).	453.30
N-(4-(4-氨基-7-甲基-5-(4-(恶唑-4-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.62 (d, J = 1.0 Hz, 1H), 8.47 (d, J = 1.0 Hz, 1H), 8.20 (s, 1H), 7.80 - 7.74 (m, 2H), 7.74 - 7.66 (m, 2H), 7.32 - 7.22 (m, 4H), 5.79 (s, 1H), 5.55 - 5.50 (m, 1H), 3.61 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	451.35

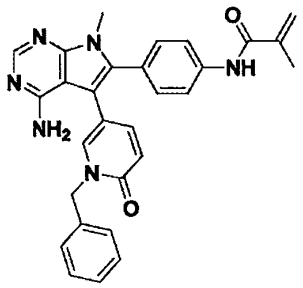
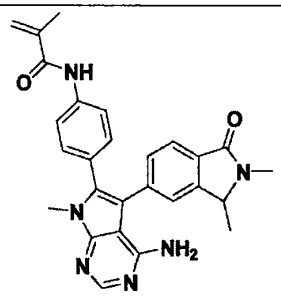
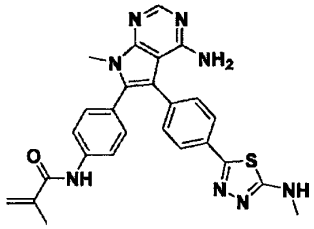
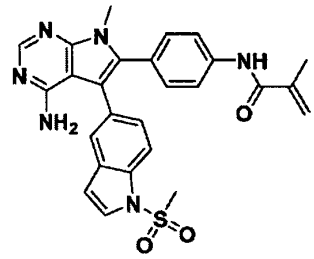
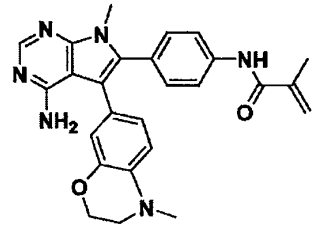
[0922]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((3-侧氧基吗啉基)甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.19 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 18.7 Hz, 6H), 6.12 - 5.75 (s, 2H), 5.55 (s, 1H), 4.55 (s, 2H), 4.15(s, 2H), 3.91 - 3.75 (s, 2H), 3.60 (s, 3H), 3.29 (s, 2H), 1.95 (s, 3H).	497.3
N-(4-(4-氨基-7-甲基-5-(6-(2-甲基-2H-四唑-5-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.45 (s, 1H), 8.24 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.84 - 7.77 (m, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.15 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 4.45 (s, 3H), 3.32 (s, 2H), 2.08 (s, 0H), 1.95 (s, 3H).	467.30
N-(4-(5-(4-(1H-咪唑-2-基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 9.88 (s, 1H), 8.21 (s, 1H), 7.92 - 7.85 (m, 2H), 7.73 - 7.67 (m, 2H), 7.32 - 7.22 (m, 5H), 7.03 (s, 1H), 5.97 - 5.90 (m, 1H), 5.79 (s, 1H), 5.53 (d, J = 2.0 Hz, 1H), 3.63 (s, 3H), 1.94 (s, 3H).	450.30
N-(4-(4-氨基-5-(6-(3-氟苯氧基)吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.20 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.76 - 7.70 (m, 2H), 7.67 (dd, J = 8.4, 2.5 Hz, 1H), 7.44 (q, J = 8.0 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.11 (dt, J = 10.4, 2.4 Hz, 1H), 7.04 (dq, J = 8.3, 3.5, 2.3 Hz, 3H), 5.80 (s, 1H), 5.54 (s, 1H), 3.60 (s, 3H), 1.96 (s, 3H).	495.15
N-(4-(4-氨基-7-甲基-5-(4-(5-(三氟甲基)-1,3,4-恶二唑-2-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.25 (s, 1H), 8.13 - 8.06 (m, 2H), 7.73 - 7.65 (m, 2H), 7.56 - 7.50 (m, 2H), 7.35 - 7.27 (m, 2H), 5.81 (s, 1H), 5.54 (d, J = 1.7 Hz, 1H), 3.72 (s, 3H), 2.04 (d, J = 1.3 Hz, 3H).	520.3

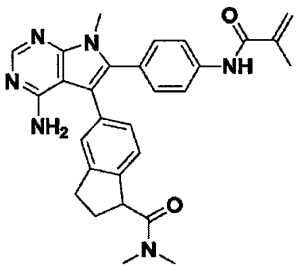
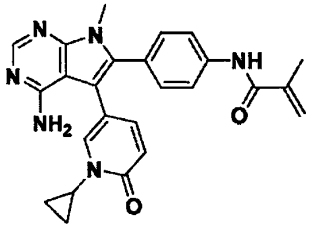
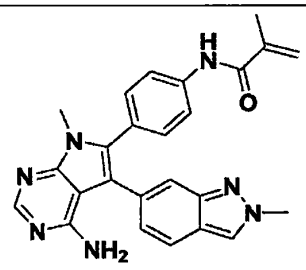
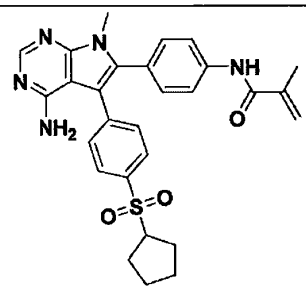
[0923]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(5-N-吗啉基吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 (d, J = 11.4 Hz, 2H), 7.79 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 2.9 Hz, 1H), 6.12 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.75 (t, J = 4.8 Hz, 4H), 3.61 (s, 3H), 3.16 (t, J = 4.9 Hz, 4H), 1.96 (s, 3H).	470.20
N-(4-(4-氨基-7-甲基-5-(6-(4-甲基-1H-吡唑-1-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.37 (s, 1H), 8.22 (s, 1H), 8.17 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.79 - 7.69 (m, 3H), 7.64 (s, 1H), 7.29 (d, J = 8.5 Hz, 2H), 6.10 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.62 (s, 3H), 2.10 (s, 3H), 1.95 (s, 3H).	465.30
N-(4-(4-氨基-7-甲基-5-(3-甲基-2-侧氧基-2,3-二氢-1H-苯并[d]咪唑-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 9.86 (s, 1H), 8.18 (s, 1H), 7.71 - 7.63 (m, 2H), 7.32 - 7.26 (m, 2H), 6.98 (d, J = 1.6 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.83 (dd, J = 7.9, 1.6 Hz, 1H), 5.79 (s, 1H), 5.55 - 5.50 (m, 1H), 3.61 (s, 3H), 3.20 (s, 3H), 1.94 (t, J = 1.2 Hz, 3H)	454.30
N-(4-(4-氨基-5-(4-(环丙基甲氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.17 (s, 1H), 7.72 - 7.65 (m, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.80 (d, J = 7.0 Hz, 2H), 3.60 (s, 3H), 1.95 (s, 3H), 1.20 (ddd, J = 12.5, 7.9, 5.0 Hz, 1H), 0.61 - 0.52 (m, 2H), 0.32 (dd, J = 4.8, 1.6 Hz, 2H).	454.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N,N-二甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.75 - 7.67 (m, 2H), 7.40 - 7.34 (m, 2H), 7.30 - 7.23 (m, 4H), 6.02 (s, 2H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.62 (s, 3H), 2.96 (s, 6H), 1.95 (d, J = 1.3 Hz, 3H).	455.20

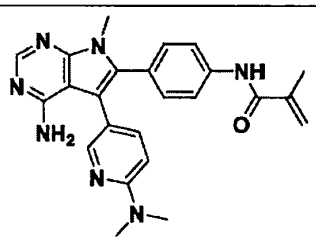
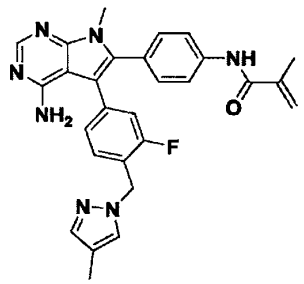
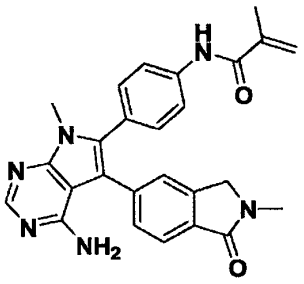
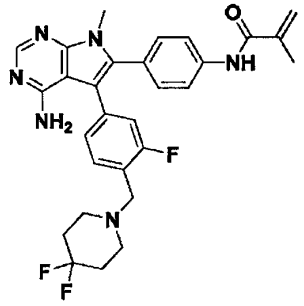
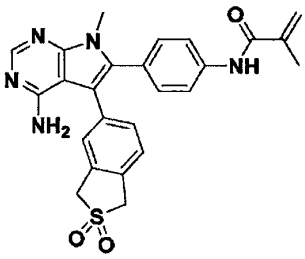
[0924]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(1-苯甲基-6-侧氧基-1,6-二氢吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.24 (s, 1H), 7.81 - 7.73 (m, 2H), 7.60 (d, J = 7.0 Hz, 1H), 7.41 - 7.26 (m, 7H), 6.49 (d, J = 1.9 Hz, 1H), 6.23 (dd, J = 7.0, 1.9 Hz, 1H), 5.85 - 5.80 (m, 1H), 5.56 (d, J = 1.8 Hz, 1H), 5.18 (s, 2H), 3.68 (s, 3H), 2.08 - 2.03 (m, 3H).	491.30
N-(4-(4-氨基-5-(2,3-二甲基-1-侧氧基异吲哚啉-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.22 (s, 1H), 7.73 - 7.66 (m, 2H), 7.59 (d, J = 7.7 Hz, 1H), 7.44 (s, 1H), 7.28 (td, J = 7.5, 6.9, 1.7 Hz, 3H), 5.79 (s, 1H), 5.53 (s, 1H), 4.50 (q, J = 6.6 Hz, 1H), 3.63 (s, 3H), 2.99 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H).	467.25
N-(4-(4-氨基-7-甲基-5-(4-(5-(甲基氨基)-1,3,4-噻二唑-2-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.87 (q, J = 4.8 Hz, 1H), 7.75 - 7.68 (m, 4H), 7.33 - 7.25 (m, 4H), 5.80 (s, 1H), 5.53 (t, J = 1.6 Hz, 1H), 3.61 (s, 3H), 2.93 (d, J = 4.8 Hz, 3H), 1.95 (d, J = 1.3 Hz, 3H).	497.20
N-(4-(4-氨基-7-甲基-5-(1-(甲基磺酰基)-1H-吲哚-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 9.85 (s, 1H), 8.20 (s, 1H), 8.01 (s, 1H), 7.70 - 7.61 (m, 3H), 7.50 (d, J = 8.4 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.14 (dd, J = 8.4, 1.7 Hz, 1H), 5.90 (s, 2H), 5.77 (s, 1H), 5.51 (t, J = 1.4 Hz, 1H), 3.63 (s, 3H), 3.02 (s, 3H), 1.93 (t, J = 1.2 Hz, 3H).	501.35
N-(4-(4-氨基-7-甲基-5-(4-甲基-3,4-二氢-2H-苯并[b][1,4]恶嗪-7-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.16 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 6.67 (s, 2H), 6.53 (s, 1H), 5.80 (s, 2H), 5.54 (s, 1H), 4.21 (t, J = 4.3 Hz, 2H), 3.31 (s, 2H), 3.24 (t, J = 4.5 Hz, 2H), 2.83 (s, 3H), 1.96 (s, 3H), 1.35 - 1.07 (m, 2H).	455.30

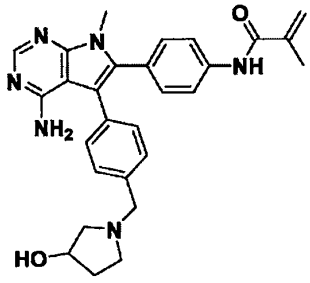
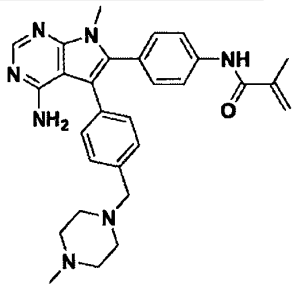
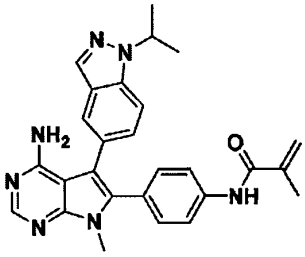
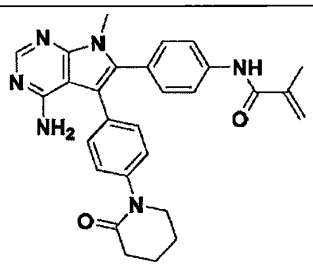
[0925]

化合物	结构	质子 NMR	MS [M+1]
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N,N-二甲基-2,3-二氢-1H-茚-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.18 (s, 1H), 7.74 - 7.66 (m, 2H), 7.33 - 7.25 (m, 2H), 7.15 (s, 1H), 7.09 - 6.98 (m, 2H), 5.80 (s, 2H), 5.53 (t, J = 1.5 Hz, 1H), 4.43 (t, J = 8.0 Hz, 1H), 3.59 (s, 3H), 3.32 (s, 3H), 3.19 (s, 4H), 2.94 (dt, J = 12.1, 4.4 Hz, 1H), 2.25 (s, 2H), 1.98 (dt, J = 16.0, 8.3 Hz, 3H).	495.3
N-(4-(4-氨基-5-(1-环丙基-6-侧氧基-1,6-二氢吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.40 (s, 1H), 7.67 (dd, J = 9.7, 3.0 Hz, 3H), 7.30 (d, J = 2.6 Hz, 1H), 7.27 (dd, J = 8.5, 2.0 Hz, 2H), 7.14 (d, J = 2.6 Hz, 1H), 6.56 (d, J = 9.3 Hz, 1H), 5.86 (s, 1H), 5.55 (q, J = 1.5 Hz, 1H), 5.07 (s, 2H), 3.72 (s, 3H), 3.33 (tt, J = 7.6, 4.2 Hz, 1H), 2.11 (d, J = 1.3 Hz, 3H), 1.12 - 1.02 (m, 2H), 0.70 - 0.61 (m, 2H).	441.15
N-(4-(4-氨基-7-甲基-5-(2-甲基-2H-吲唑-6-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 7.71 - 7.62 (m, 3H), 7.42 (q, J = 1.2 Hz, 1H), 7.33 - 7.25 (m, 2H), 6.88 (dd, J = 8.5, 1.4 Hz, 1H), 5.78 (t, J = 1.1 Hz, 1H), 5.54 - 5.49 (m, 1H), 4.15 (s, 3H), 3.63 (s, 3H), 1.93 (t, J = 1.2 Hz, 3H).	438.15
N-(4-(4-氨基-5-(4-(环戊基磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.23 (s, 1H), 7.84 - 7.77 (m, 2H), 7.75 - 7.68 (m, 2H), 7.47 - 7.40 (m, 2H), 7.27 - 7.21 (m, 2H), 6.01 (s, 0H), 5.80 (s, 1H), 5.54 (s, 1H), 3.82 - 3.70 (m, 1H), 3.62 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H), 1.84 (d, J = 8.8 Hz, 4H), 1.57 (q, J = 6.7, 6.1 Hz, 4H).	516.25

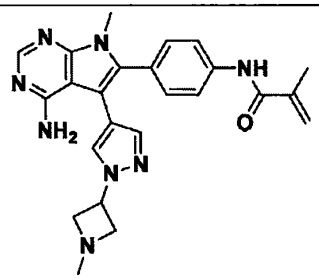
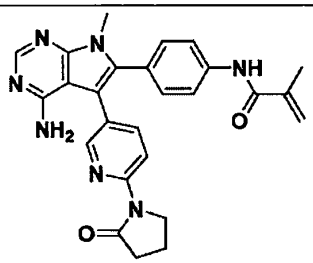
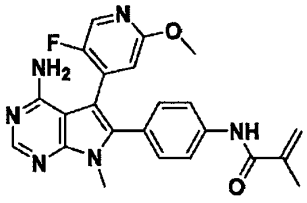
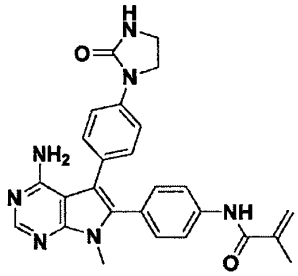
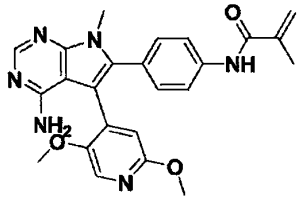
[0926]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(6-(二甲基氨基)吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.18 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.37 (dd, J = 8.7, 2.5 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.7 Hz, 1H), 5.80 (s, 1H), 5.72 (s, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 3.01 (s, 6H), 1.95 (s, 3H).	428.35
N-(4-(4-氨基-5-(3-氟-4-((4-甲基-1H-吡唑-1-基)甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 7.30 - 7.24 (m, 3H), 7.02 (d, J = 11.5 Hz, 3H), 5.92 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 5.29 (s, 2H), 3.58 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H).	496.35
N-(4-(4-氨基-7-甲基-5-(2-甲基-1-侧氧基异吲哚啉-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.21 (s, 1H), 7.72 - 7.65 (m, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.1 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 5.79-5.76 (s, 2H), 5.53 (d, J = 1.9 Hz, 1H), 4.45 (s, 2H), 3.62 (s, 3H), 3.06 (s, 3H), 1.94 (s, 3H).	453.20
N-(4-(4-氨基-5-(4-((4,4-二氟哌啶-1-基)甲基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (d, J = 1.9 Hz, 1H), 7.68 (dd, J = 8.7, 2.0 Hz, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.29 (dd, J = 8.7, 2.0 Hz, 2H), 7.13 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 10.8 Hz, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 3.72 - 3.65 (m, 5H), 3.33 (d, J = 9.1 Hz, 1H), 2.64 (d, J = 6.6 Hz, 4H), 2.07 - 1.95 (m, 7H).	535.40
N-(4-(4-氨基-5-(2,2-二氧离子基-1,3-二氢苯并[c]噻吩-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.36 - 7.25 (m, 4H), 7.19 (dd, J = 7.8, 1.8 Hz, 1H), 5.80 (s, 1H), 5.54 (d, J = 2.0 Hz, 1H), 4.48 (d, J = 4.6 Hz, 4H), 3.60 (s, 3H), 1.95 (s, 3H).	474.15

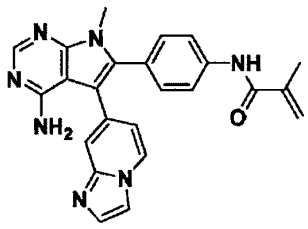
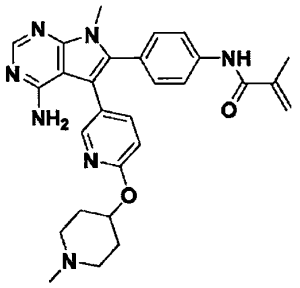
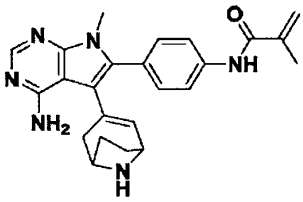
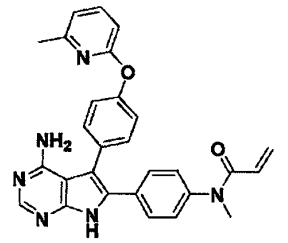
[0927]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((3-羟基吡咯烷-1-基)甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.19 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.27 (dd, J = 8.2, 4.7 Hz, 4H), 7.19 (d, J = 7.7 Hz, 2H), 5.86 (s, 2H), 5.53 (s, 1H), 4.67 (d, J = 4.6 Hz, 1H), 4.19 (d, J = 7.1 Hz, 1H), 3.61 (s, 3H), 3.54 (d, J = 5.5 Hz, 2H), 2.67 (dd, J = 9.6, 6.2 Hz, 1H), 2.57 (t, J = 7.7 Hz, 1H), 2.40 (q, J = 7.5 Hz, 1H), 2.30 (dd, J = 9.8, 3.6 Hz, 1H), 2.06 - 1.95 (m, 4H), 1.65 - 1.41 (m, 1H).	483.3
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基哌嗪-1-基)甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.46 (s, 1H), 8.21 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.28 (t, J = 8.1 Hz, 4H), 5.81 (s, 1H), 5.55 (s, 1H), 3.68 (d, J = 18.2 Hz, 5H), 3.03 (s, 4H), 2.69 (s, 7H), 2.04 (s, 3H).	496.35
N-(4-(4-氨基-5-(1-异丙基-1H-吲唑-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.19 (s, 1H), 8.04 (s, 1H), 7.70 - 7.61 (m, 4H), 7.28 (d, J = 8.6 Hz, 2H), 7.21 (dd, J = 8.6, 1.6 Hz, 1H), 5.77 (s, 2H), 5.51 (s, 1H), 4.97 (p, J = 6.6 Hz, 1H), 3.62 (s, 3H), 1.93 (s, 3H), 1.49 (d, J = 6.6 Hz, 6H).	466.30
N-(4-(4-氨基-7-甲基-5-(4-(2-侧氧基哌啶-1-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.75 - 7.67 (m, 2H), 7.41 - 7.21 (m, 6H), 5.85 (m, 2H), 5.55 (d, J = 1.2 Hz, 1H), 3.65 (d, J = 8.1 Hz, 5H), 2.55 - 2.31 (t, J = 6.3 Hz, 2H), 1.95 (t, J = 1.2 Hz, 3H), 1.91 - 1.77 (m, 4H).	481.3

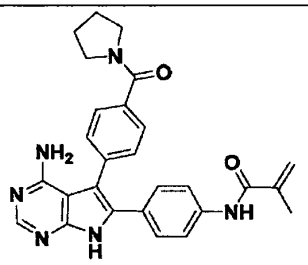
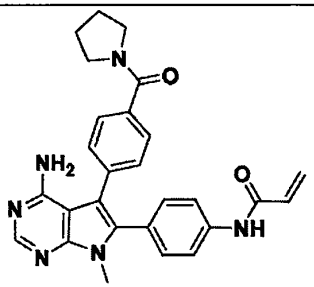
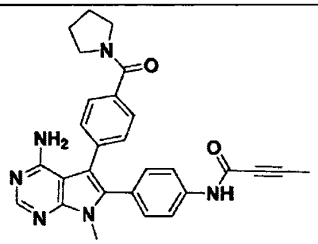
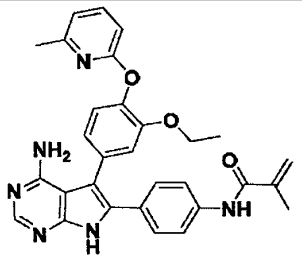
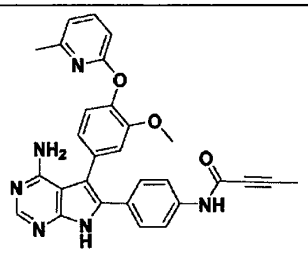
[0928]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-(1-甲基氮杂环丁-3-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.38 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.56 (s, 1H), 7.50 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 5.84 (s, 1H), 5.53 (d, *J* = 1.8 Hz, 1H), 5.08 (s, 2H), 4.87 (p, *J* = 6.9 Hz, 1H), 3.86 - 3.75 (m, 2H), 3.70 (s, 3H), 3.54 - 3.45 (m, 2H), 2.45 (s, 3H), 2.11 (s, 3H).	443.20
N-(4-(4-氨基-7-甲基-5-(6-(2-侧氧基吡咯烷-1-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.23 - 8.14 (m, 2H), 7.75 - 7.63 (m, 3H), 7.28 (d, *J* = 8.3 Hz, 2H), 5.95 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.97 (t, *J* = 7.1 Hz, 2H), 3.61 (s, 3H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.04 (q, *J* = 7.5 Hz, 2H), 1.95 (s, 3H).	468.35
N-(4-(4-氨基-5-(5-氟-2-甲氧基吡啶-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.21 (s, 1H), 8.04 (d, *J* = 1.4 Hz, 1H), 7.75 - 7.69 (m, 2H), 7.30 - 7.23 (m, 2H), 6.70 (d, *J* = 5.0 Hz, 1H), 6.16 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 1.95 (s, 3H).	433.20
N-(4-(4-氨基-7-甲基-5-(4-(2-侧氧基咪唑啶-1-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.18 (s, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.31 - 7.24 (m, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.96 (s, 1H), 5.94 (s, 2H), 5.79 (s, 1H), 5.55 - 5.50 (m, 1H), 3.84 (dd, *J* = 9.2, 6.6 Hz, 2H), 3.40 (t, *J* = 7.9 Hz, 3H), 3.32 (s, 2H), 1.95 (s, 3H).	468.30
N-(4-(4-氨基-5-(2,5-二甲氧基吡啶-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.18 (s, 1H), 7.87 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.51 (s, 1H), 5.88 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.76 (s, 3H), 3.60 (d, *J* = 2.3 Hz, 6H), 1.95 (s, 3H).	445.25

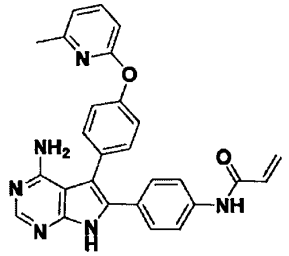
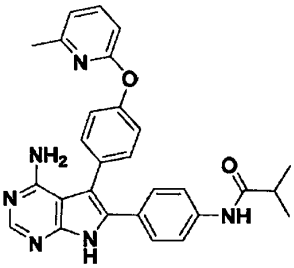
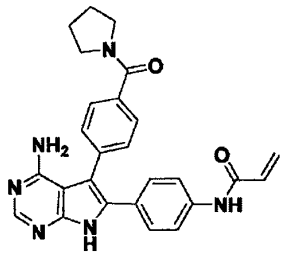
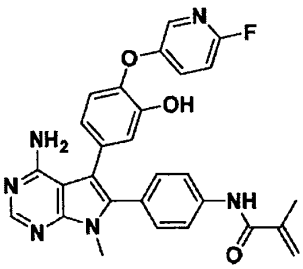
[0929]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(咪唑并[1,2-a]吡啶-7-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.44 (d, J = 7.0 Hz, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.56 - 7.51 (m, 1H), 7.36 - 7.28 (m, 3H), 6.63 (dd, J = 7.0, 1.7 Hz, 1H), 6.15 (s, 2H), 5.78 (d, J = 11.5 Hz, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 1.94 (s, 3H).	424.25
N-(4-(4-氨基-7-甲基-5-(6-(1-甲基哌啶-4-基氧基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.97 (d, J = 2.5 Hz, 1H), 7.75 - 7.70 (m, 2H), 7.52 (dd, J = 8.5, 2.5 Hz, 1H), 7.32 - 7.24 (m, 2H), 6.75 (d, J = 8.5 Hz, 1H), 5.92 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 4.95 (tt, J = 8.8, 4.1 Hz, 1H), 3.60 (s, 3H), 2.66 (dd, J = 12.9, 5.5 Hz, 2H), 2.19 - 2.08 (m, 5H), 1.99 - 1.93 (m, 5H), 1.69 (ddt, J = 14.5, 9.2, 4.8 Hz, 2H).	498.25
N-(4-(4-氨基-5-(8-氮杂双环[3.2.1]辛-2-烯-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.37 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 6.21 (d, J = 5.6 Hz, 1H), 5.87 (s, 1H), 5.60 (s, 1H), 4.37 (t, J = 5.5 Hz, 1H), 4.10 (s, 1H), 3.75 (s, 3H), 2.93 - 2.84 (m, 1H), 2.31 - 2.12 (m, 4H), 2.07 (s, 3H), 1.99 - 1.90 (m, 1H), 1.57 (s, 1H), 1.30 (d, J = 13.5 Hz, 1H).	415.30
N-(4-(4-氨基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-N-甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 8.14 (s, 1H), 7.74-7.78 (m, 1H), 7.41-7.47 (m, 4H), 7.21-7.24 (m, 4H), 6.84-6.86 (d, J = 8 Hz, 1H), 5.17-6.18 (m, 5H), 3.23 (s, 3H), 2.36 (s, 3H).	477.35

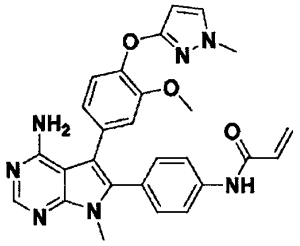
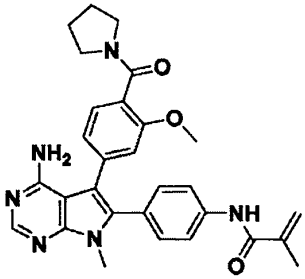
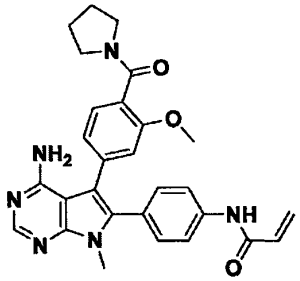
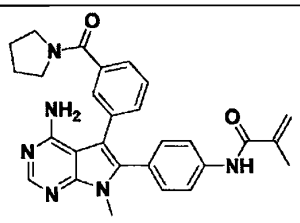
[0930]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 12.12 (s, 1H), 9.82 (s, 1H), 8.13 (s, 1H), 7.59 (d, J = 8.3 Hz, 4H), 7.39 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 5.79 (s, 1H), 5.52 (s, 1H), 3.48 (dt, J = 11.2, 6.4 Hz, 4H), 1.96 - 1.81 (m, 7H).	467.30
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.21 (s, 1H), 7.72 - 7.65 (m, 2H), 7.55 - 7.46 (m, 2H), 7.28 (dd, J = 8.6, 6.8 Hz, 4H), 6.44 (dd, J = 17.0, 10.2 Hz, 1H), 6.27 (dd, J = 17.0, 2.2 Hz, 1H), 5.78 (dd, J = 10.2, 2.2 Hz, 2H), 3.62 (s, 3H), 3.44 (dt, J = 17.8, 6.6 Hz, 4H), 1.84 (ddd, J = 17.8, 12.8, 6.8 Hz, 4H).	467.20
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-炔酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.21 (s, 2H), 7.59 -7.61 (d, J = 8 Hz, 2H), 7.47-7.49 (d, J = 8 Hz, 2H), 7.26 (m, 4H), 5.91 (s, 1H), 3.59 (s, 3H), 3.16-3.45 (m, 4H), 2.05 (s, 3H), 1.82-1.86 (m, 4H).	479.35
N-(4-(4-氨基-5-(3-乙氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 12.05 (s, 1H), 9.83 (s, 1H), 8.13 (s, 1H), 7.70 (m, 1H), 7.66 - 7.60 (m, 2H), 7.39 - 7.30 (m, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 7.01 - 6.90 (m, 2H), 6.74 (d, J = 8.4 Hz, 1H), 5.79 (s, 2H), 5.53 (s, 1H), 3.93-3.88 (m, 2H), 2.34 (s, 3H), 1.95 (s, 3H), 1.23 - 1.13 (m, 3H).	521.25
N-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-炔酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 12.07 (s, 1H), 10.66 (s, 1H), 8.13 (s, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.37 - 7.25 (m, 2H), 7.17 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 7.04 - 6.88 (m, 2H), 6.72 (d, J = 8.4 Hz, 1H), 5.84 (s, 2H), 3.62 (s, 3H), 2.34 (s, 3H), 2.05 (s, 3H).	505.25

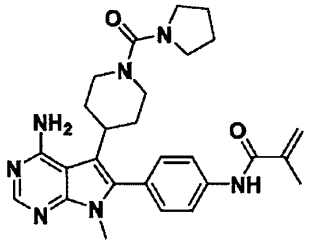
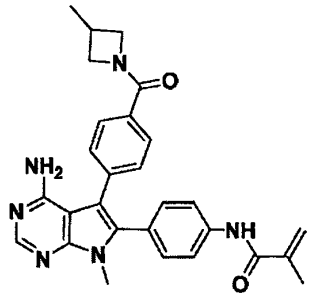
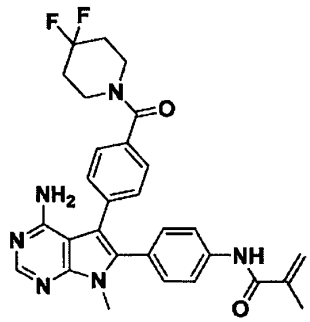
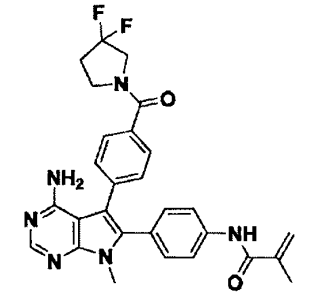
[0931]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 10.19 (s, 1H), 8.12 (s, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.42 - 7.35 (m, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.23 - 7.16 (m, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.43 (dd, J = 17.0, 10.1 Hz, 1H), 6.26 (dd, J = 17.0, 2.0 Hz, 1H), 5.76 (dd, J = 10.1, 2.0 Hz, 1H), 2.38 (s, 3H).	463.4
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)异丁酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.87 (s, 1H), 8.12 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.40 - 7.33 (m, 2H), 7.31 - 7.25 (m, 2H), 7.22 - 7.15 (m, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.74 (s, 2H), 2.59 (q, J = 6.7 Hz, 1H), 2.38 (s, 3H), 1.09 (d, J = 6.8 Hz, 6H).	479.4
N-(4-(4-氨基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.20 (s, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.73 - 7.67 (m, 2H), 7.34 - 7.23 (m, 4H), 7.15 - 7.08 (m, 2H), 6.89 (d, J = 8.6 Hz, 1H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 16.9, 2.0 Hz, 1H), 5.96 (s, 2H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.62 (s, 3H), 2.40 (s, 3H).	453.30
N-(4-(4-氨基-5-(4-((6-氟吡啶-3-基)氧基)-3-羟基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.61 (s, 1H), 8.23 - 8.10 (m, 2H), 7.81 - 7.71 (m, 3H), 7.31 (d, J = 8.4 Hz, 2H), 7.09 - 6.96 (m, 2H), 6.81 (d, J = 2.2 Hz, 1H), 6.70 (dd, J = 8.0, 2.2 Hz, 1H), 5.81 (s, 1H), 3.60 (s, 3H), 1.96 (s, 3H).	511.20

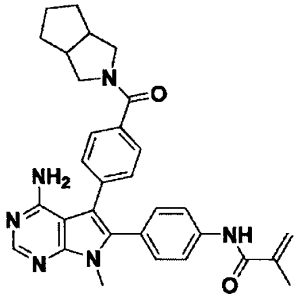
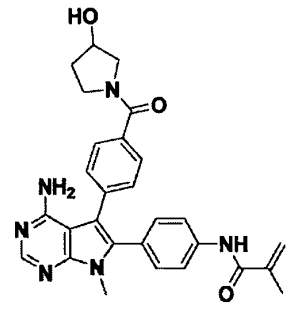
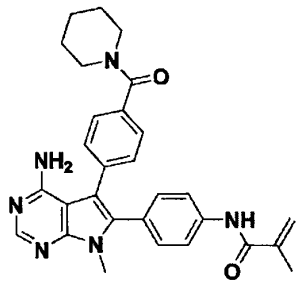
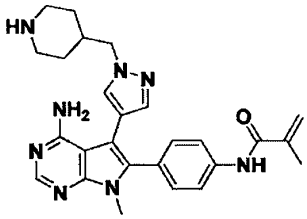
[0932]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.19 (d, J = 2.2 Hz, 1H), 7.78 - 7.60 (m, 3H), 7.55 (d, J = 2.3 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.01 - 6.95 (m, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.75 (m, J = 8.2, 2.2 Hz, 1H), 6.45 (m, J = 17.0, 10.1 Hz, 1H), 6.21 - 6.12 (m, 1H), 5.78 (dd, J = 10.1, 2.0 Hz, 1H), 5.69 (d, J = 2.3 Hz, 1H), 3.71 (s, 3H), 3.62 (d, J = 9.0 Hz, 6H).	496.20
N-(4-(4-氨基-5-(3-甲氧基-4-(吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 7.6 Hz, 1H), 6.90 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H) , 6.11 (s, 1H), 5.82 (s, 1H), 5.54 (s, 1H), 3.63 (d, J = 12.4 Hz, 6H), 3.43 (t, J = 6.8 Hz, 2H), 3.16-3.13 (m, 2H), 1.96 (s, 3H), 1.87-1.77 (m, 4H).	511.35
N-(4-(4-氨基-5-(3-甲氧基-4-(吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.21 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 1.5 Hz, 1H), 6.82 (dd, J = 7.7, 1.4 Hz, 1H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 6.02 (s, 2H), 5.78 (dd, J = 10.0, 2.0 Hz, 1H), 3.62 (d, J = 6.3 Hz, 6H), 3.42 (t, J = 6.9 Hz, 2H), 3.13 (t, J = 6.5 Hz, 2H), 1.82 (dq, J = 19.6, 7.0 Hz, 4H).	497.3
N-(4-(4-氨基-7-甲基-5-(3-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.21 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.53 - 7.35 (m, 3H), 7.25 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 2.0 Hz, 1H), 5.78 (s, 1H), 5.54 (s, 1H), 3.61 (s, 3H), 3.37 (t, J = 7.0 Hz, 2H), 2.84 (t, J = 6.6 Hz, 2H), 1.95 (s, 3H), 1.81 - 1.73 (m, 2H), 1.67 - 1.59 (m, 2H).	481.35

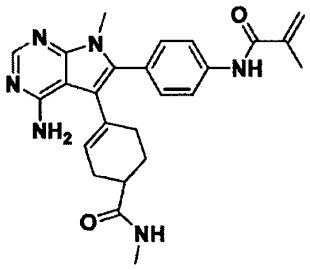
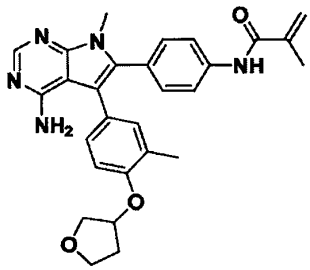
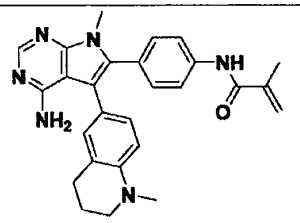
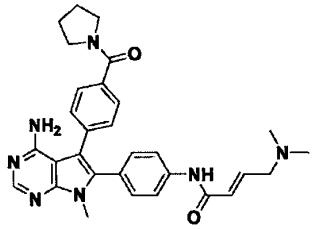
[0933]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-(吡咯烷-1-羰基)哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.98 (s, 1H), 8.11 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 6.38 (s, 2H), 5.83 (s, 1H), 5.56 (s, 1H), 3.60 (d, J = 12.7 Hz, 2H), 3.36 (s, 3H), 3.18 (d, J = 6.3 Hz, 4H), 3.05 (s, 1H), 2.73 (t, J = 12.3 Hz, 2H), 1.98 (s, 3H), 1.72 (d, J = 4.9 Hz, 4H), 1.68 - 1.49 (m, 4H).	488.25
N-(4-(4-氨基-7-甲基-5-(4-(3-甲基氮杂环丁烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.63 - 7.57 (m, 2H), 7.27 (t, J = 8.4 Hz, 4H), 5.80 (s, 1H), 5.53 (t, J = 1.6 Hz, 1H), 4.42 (t, J = 8.3 Hz, 1H), 4.15 (t, J = 8.8 Hz, 1H), 3.88 (s, 1H), 3.61 (s, 3H), 3.32 (s, 1H), 2.75 - 2.66 (m, 1H), 1.95 (d, J = 1.2 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H).	481.20
N-(4-(4-氨基-5-(4-(4,4-二氟哌啶-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.81 - 7.64 (m, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.34 - 7.18 (m, 4H), 5.80 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 2.09 - 1.97 (m, 4H), 1.95 (d, J = 1.3 Hz, 3H).	531.20
N-(4-(4-氨基-5-(4-(3,3-二氟吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.51 (s, 2H), 7.30 - 7.23 (m, 2H), 5.98 (s, 2H), 5.80 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 3.93 (s, 2H), 3.72 (t, J = 7.4 Hz, 2H), 3.61 (s, 3H), 2.50 - 2.32 (m, 2H), 1.95 (d, J = 1.2 Hz, 3H).	517.35

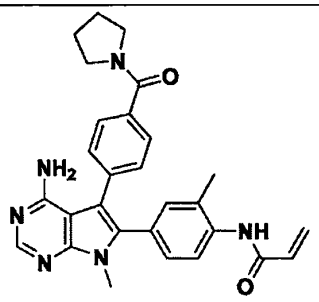
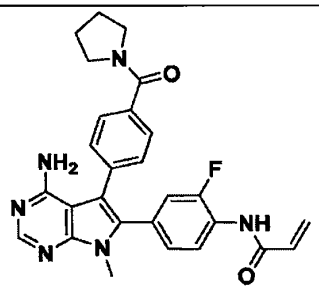
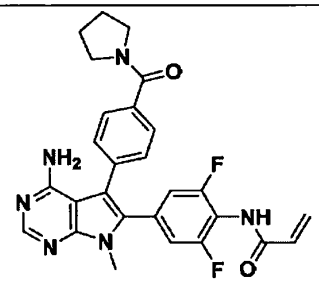
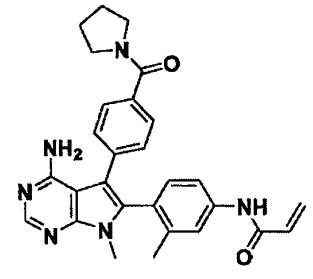
[0934]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(十氢环戊并[c]吡咯-2-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.26 (dd, J = 8.4, 2.1 Hz, 4H), 5.93 (s, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 3.69 (s, 1H), 3.61 (s, 4H), 3.22 (s, 2H), 2.62 (s, 2H), 1.95 (s, 3H), 1.84 - 1.60 (m, 3H), 1.60 - 1.20 (m, 3H).	521.30
N-(4-(4-氨基-5-(4-(3-羟基吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.49 (dd, J = 8.3, 2.3 Hz, 2H), 7.27 (dd, J = 8.3, 1.8 Hz, 4H), 5.80 (s, 3H), 5.53 (t, J = 1.5 Hz, 1H), 4.96 (dd, J = 27.0, 3.5 Hz, 1H), 4.28 (d, J = 36.6 Hz, 1H) , 3.66 (s, 3H), 3.32 (s, 3H), 3.24 (d, J = 11.0 Hz, 1H), 1.95 (t, J = 1.2 Hz, 5H).	497.35
N-(4-(4-氨基-7-甲基-5-(4-(哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.68 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 8.3, 1.4 Hz, 4H), 5.95 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.68 - 3.36 (m, 7H), 1.96 (t, J = 1.2 Hz, 3H), 1.62 (d, J = 6.4 Hz, 2H), 1.51 (s, 4H).	495.35
N-(4-(4-氨基-7-甲基-5-(1-(哌啶-4-基甲基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.37 (s, 1H), 7.77 - 7.70 (m, 2H), 7.59 (s, 1H), 7.54 (s, 1H), 7.40 - 7.33 (m, 2H), 5.84 (s, 1H), 5.58 (d, J = 1.8 Hz, 1H), 4.10 (d, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.46 - 3.37 (m, 2H), 2.96 (td, J = 12.9, 3.0 Hz, 2H), 2.16 (ddd, J = 11.4, 7.6, 3.9 Hz, 1H), 2.06 (s, 3H), 1.72 - 1.63 (m, 2H), 1.55 - 1.25 (m, 2H).	471.35

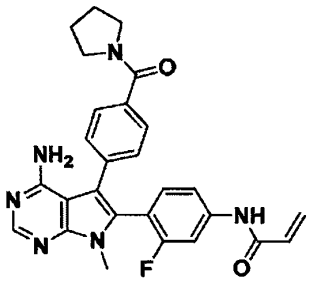
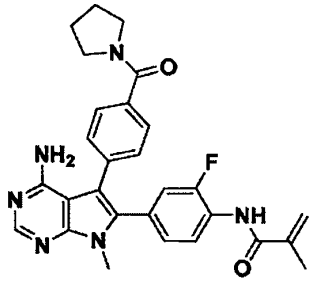
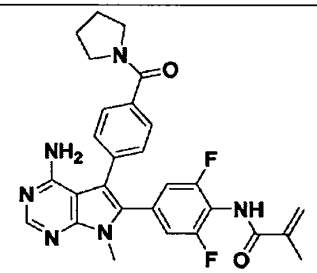
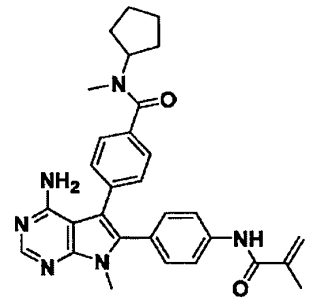
[0935]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.10 (s, 1H), 7.84 - 7.75 (m, 3H), 7.46 - 7.39 (m, 2H), 5.83 (s, 1H), 5.77 (s, 1H), 5.56 (d, J = 1.6 Hz, 1H), 3.57 (s, 3H), 2.57 (d, J = 4.5 Hz, 3H), 2.45 (q, J = 6.2 Hz, 1H), 2.29 (s, 1H), 2.24 (s, 1H), 1.98 (t, J = 1.2 Hz, 3H), 1.89 (s, 2H), 1.65 (d, J = 6.3 Hz, 2H).	445.30
N-(4-(4-氨基-7-甲基-5-(3-甲基-4-(四氢呋喃-3-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.17 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.07 (s, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 5.00 (d, J = 5.8 Hz, 1H), 3.94 - 3.72 (m, 4H), 3.59 (s, 3H), 2.20 (dq, J = 14.5, 7.7 Hz, 1H), 2.09 (s, 3H), 1.99 (d, J = 7.1 Hz, 1H), 1.95 (s, 3H), 1.16 (t, J = 13.1 Hz, 1H).	484.35
N-(4-(4-氨基-7-甲基-5-(1-甲基-1,2,3,4-四氢喹啉-6-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.15 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 6.86 (dd, J = 8.3, 2.2 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 3.58 (s, 3H) 3.20 (t, J = 5.6 Hz, 2H), 2.82 (s, 3H), 2.63 (t, J = 6.5 Hz, 2H), 1.95 (s, 3H), 1.87 (p, J = 6.2 Hz, 2H).	453.40
(E)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-(二甲基氨基)丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.20 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.26 (dd, J = 8.3, 1.9 Hz, 4H), 6.74 (dt, J = 15.5, 5.8 Hz, 1H), 6.31 - 6.23 (m, 1H), 5.92 (s, 1H), 3.61 (s, 3H), 3.43 (dt, J = 17.9, 6.6 Hz, 4H), 3.28 (s, 1H), 3.09 - 3.03 (m, 1H), 2.18 (s, 6H), 1.89 - 1.78 (m, 4H).	524.45

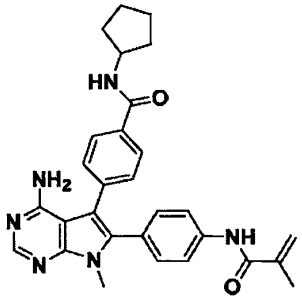
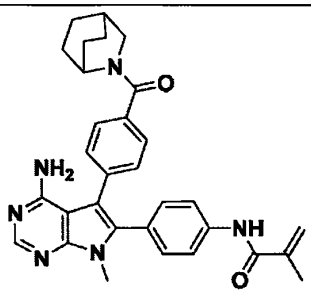
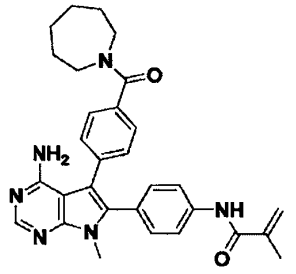
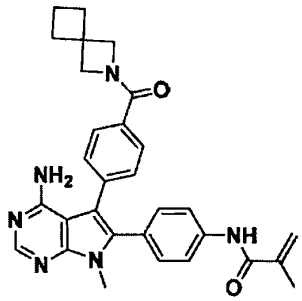
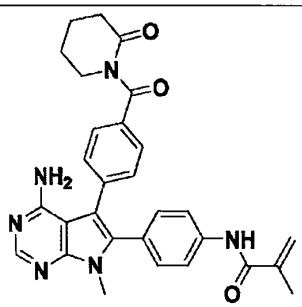
[0936]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.21 (s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 8.2, 2.1 Hz, 1H), 6.56 (dd, J = 16.9, 10.2 Hz, 1H), 6.26 (dd, J = 17.0, 2.0 Hz, 1H), 5.76 (dd, J = 10.1, 2.0 Hz, 2H), 3.43 (dt, J = 21.9, 6.5 Hz, 4H), 3.33 (s, 3H), 2.18 (s, 3H), 1.84 (dq, J = 18.5, 7.1 Hz, 4H).	481.45
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氟苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.22 (s, 1H), 8.08 (t, J = 8.3 Hz, 1H), 7.54 - 7.48 (m, 2H), 7.32 - 7.23 (m, 3H), 7.14 (dd, J = 8.3, 1.9 Hz, 1H), 6.64 (dd, J = 17.0, 10.2 Hz, 1H), 6.29 (dd, J = 17.0, 2.0 Hz, 1H), 5.79 (dd, J = 10.1, 2.0 Hz, 1H), 3.62 (s, 3H), 3.44 (dt, J = 19.1, 6.5 Hz, 4H), 1.85 (dp, J = 18.1, 6.7 Hz, 4H).	485.1
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,6-二氟苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.23 (s, 1H), 7.53 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.55 - 6.40 (m, 1H), 6.27 (dd, J = 17.2, 1.9 Hz, 1H), 5.82 (dd, J = 10.2, 1.9 Hz, 2H), 3.69 (s, 3H), 3.48 (q, J = 9.0, 6.9 Hz, 2H), 3.41 (t, J = 6.5 Hz, 2H), 1.90 - 1.79 (m, 4H).	503.35
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.21 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.49 - 7.42 (m, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.24 - 7.18 (m, 2H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.77 (dd, J = 10.0, 2.1 Hz, 1H), 3.41 (d, J = 6.3 Hz, 7H), 1.91 (s, 3H), 1.83 (dt, J = 18.0, 6.5 Hz, 4H).	481.2

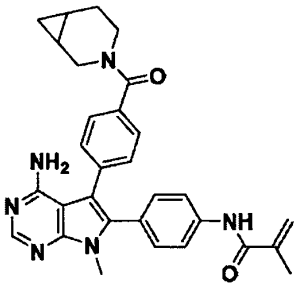
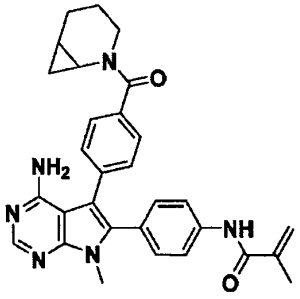
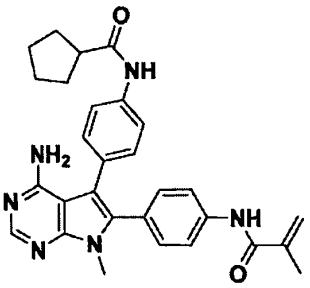
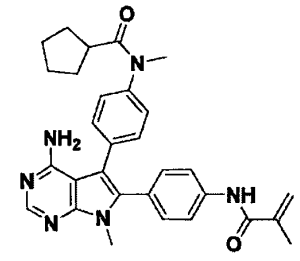
[0937]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.22 (s, 1H), 7.79 (dd, J = 12.2, 2.0 Hz, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.37 (dd, J = 8.5, 2.0 Hz, 1H), 7.32 - 7.24 (m, 2H), 7.24 (s, 1H), 6.43 (dd, J = 17.0, 10.0 Hz, 1H), 6.30 (dd, J = 17.0, 2.0 Hz, 1H), 6.03 (s, 2H), 5.82 (dd, J = 10.1, 2.1 Hz, 1H), 3.55 (s, 3H), 3.43 (dt, J = 18.4, 6.6 Hz, 4H), 1.83 (dq, J = 12.9, 6.8 Hz, 4H).	485.35
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.22 (s, 1H), 7.59 (t, J = 8.2 Hz, 1H), 7.54 - 7.47 (m, 2H), 7.32 - 7.24 (m, 3H), 7.13 (dd, J = 8.3, 1.9 Hz, 1H), 5.88 (s, 1H), 5.56 (s, 1H), 3.65 (s, 3H), 3.44 (dt, J = 16.9, 6.5 Hz, 4H), 1.95 (s, 3H), 1.84 (dq, J = 18.5, 7.0 Hz, 4H).	499.2
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,6-二氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.23 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.23 - 7.13 (m, 2H), 5.91 (s, 1H), 5.60 (s, 1H), 3.44 (dt, J = 19.8, 6.5 Hz, 4H), 3.33 (s, 2H), 1.94 (s, 3H), 1.84 (dq, J = 18.4, 6.7 Hz, 3H).	517.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环戊基-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.73 - 7.67 (m, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.26 (dd, J = 8.4, 2.4 Hz, 4H), 6.33 - 5.71 (s, 3H), 5.53 (d, J = 1.8 Hz, 1H), 4.99 - 3.92 (s, 1H), 3.65 (s, 3H), 2.82 (s, 3H), 1.95 (d, J = 1.6 Hz, 3H), 1.90 - 1.58 (s, 6H), 1.57 - 1.33 (s, 2H).	509.4

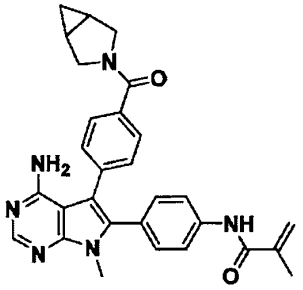
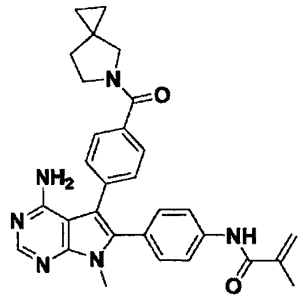
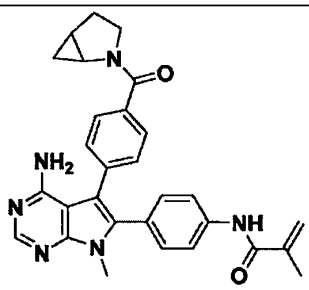
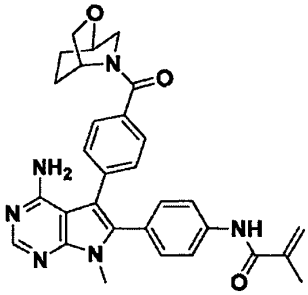
[0938]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环戊基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.29 - 8.19 (m, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.79 - 7.66 (m, 2H), 7.27 (t, J = 8.4 Hz, 4H), 6.31 - 5.45(s, 4H), 4.22 (q, J = 6.9 Hz, 1H), 3.65 (s, 3H), 1.95 (t, J = 1.2 Hz,3H), 1.87 (s, 2H), 1.69 (s, 2H), 1.53 (q, J = 11.7, 8.4 Hz, 4H).	495.35
N-(4-(5-(4-(2-氮杂双环[2.2.2]辛烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.71 - 7.64 (m, 2H), 7.44 - 7.35 (m, 4H), 7.28 (dd, J = 9.4, 2.7 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.70 (s, 4H), 3.58 (d, J = 2.5 Hz, 2H), 2.08 - 2.02 (m, 4H), 1.92 (s, 2H), 1.81 - 1.68 (m, 6H).	521.40
N-(4-(4-氨基-5-(4-(氮杂环庚烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.73 - 7.67 (m, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.25 (dd, J = 8.3, 1.6 Hz, 4H), 5.93 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.62 (s, 3H), 3.55 (t, J = 5.7 Hz, 2H), 1.95 (d, J = 1.5 Hz, 3H), 1.70 (s, 2H), 1.55 (s, 6H).	509.4
N-(4-(5-(4-(2-氮杂螺[3.3]庚烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.74 - 7.68 (m, 2H), 7.62 - 7.56 (m, 2H), 7.31 - 7.23 (m, 4H), 5.80 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 4.29 (s, 2H), 4.00 (s, 2H), 3.61 (s, 3H), 2.15 (t, J = 7.6 Hz, 4H), 1.95 (s, 3H), 1.86 (s, 1H), 1.76 (td, J = 7.8, 3.7 Hz, 2H).	507.40
N-(4-(4-氨基-7-甲基-5-(4-(2-侧氧基哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.21 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 8.2, 5.8 Hz, 4H), 5.80 (s, 1H), 5.70 (s, 2H), 5.53 (s, 1H), 3.67 (t, J = 5.7 Hz, 2H), 3.61 (s, 3H), 2.50(s,2H)1.95 (s, 3H), 1.87 (tt, J = 11.7, 6.3 Hz, 4H).	509.25

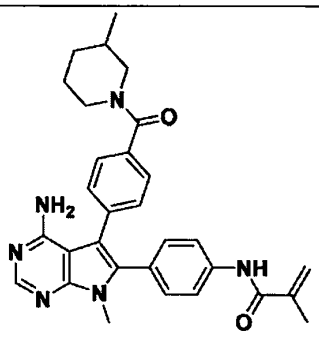
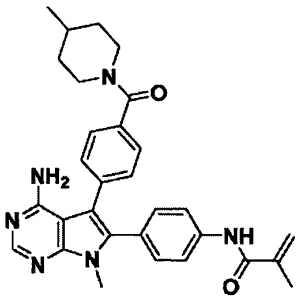
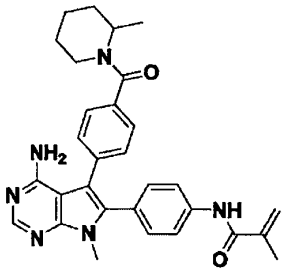
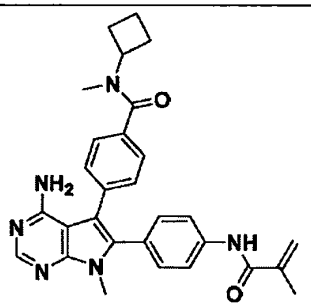
[0939]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-(4-(3-氮杂双环[4.1.0]庚烷-3-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 8.3 Hz, 4H), 5.95 (s, 2H), 5.80 (s, 1H), 5.53 (d, J = 1.7 Hz, 1H), 3.68 (d, J = 12.5 Hz, 2H), 3.61 (s, 4H), 3.08 (s, 1H), 1.95 (s, 4H), 1.70 - 1.64 (m, 1H), 1.06 (s, 2H), 0.64 (s, 1H), 0.21 (s, 1H).	507.40
N-(4-(5-(4-(2-氮杂双环[4.1.0]庚烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.73 - 7.66 (m, 2H), 7.52 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.26 (dd, J = 8.2, 4.2 Hz, 4H), 6.25 - 5.70 (s, 3H), 5.53 (t, J = 1.5 Hz, 1H), 4.05 (d, J = 12.6 Hz, 1H), 3.65 (d, J = 7.1 Hz, 3H), 3.02 (t, J = 12.6 Hz, 1H),2.52 (t, J = 12.6 Hz, 1H), 1.95 (s, 3H), 1.85 (s, 2H), 1.83 - 1.55 (m, 1H), 1.35 (d, J = 13.8 Hz, 2H), 0.37 (s, 1H).	507.4
N-(4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)环戊烷甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (d, J = 11.0 Hz, 2H), 8.18 (s, 1H), 7.72 - 7.65 (m, 2H), 7.62 - 7.55 (m, 2H), 7.29 - 7.22 (m, 2H), 7.18 - 7.11 (m, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 2.76 (p, J = 7.8 Hz, 1H), 1.95 (d, J = 1.5 Hz, 3H), 1.85 (ddd, J = 14.1, 8.3, 4.3 Hz, 2H), 1.77 - 1.62 (m, 4H), 1.61 - 1.51 (m, 2H).	495.20
N-(4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)-N-甲基环戊烷甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.80 - 7.62 (m, 2H), 7.36 - 7.19 (m, 6H), 5.78 (s, 1H), 5.53 (s, 1H), 3.63 (s, 3H), 3.17 (d, J = 2.9 Hz, 3H), 1.94 (t, J = 1.2 Hz, 3H), 1.65 - 1.30 (s, 9H).	509.30

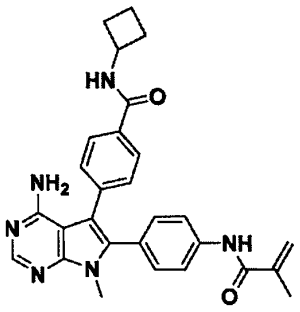
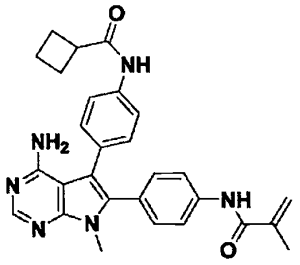
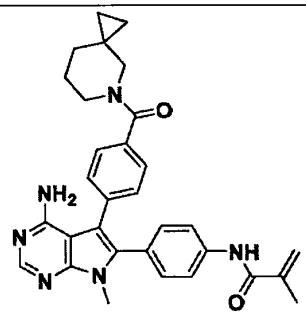
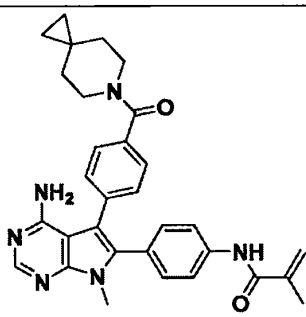
[0940]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-(4-(3-氮杂双环[3.1.0]己烷-3-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.26 (dd, J = 8.2, 4.4 Hz, 4H), 6.25 - 5.75 (s, 2H), 5.53 (s, 1H), 3.95 (d, J = 11.9 Hz, 1H), 3.66 (d, J = 10.7 Hz, 1H), 3.58 (s, 3H), 3.38 (d, J = 10.8 Hz, 2H), 1.95 (s, 3H), 1.69 - 1.51 (m, 2H), 0.65 (q, J = 4.3 Hz, 1H) , 0.08 (q, J = 4.3 Hz, 1H).	493.35
N-(4-(5-(4-(5-氮杂螺[2.4]庚烷-5-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.70 (dd, J = 8.8, 3.4 Hz, 2H), 7.50 (dd, J = 12.8, 7.8 Hz, 2H), 7.26 (dt, J = 8.2, 4.5 Hz, 4H), 6.04 (s, 1H), 5.92- 5.80 (s, 1H), 5.53 (s, 1H), 3.66 - 3.55 (m, 5H), 3.37 (d, J = 8.4 Hz, 2H), 1.95 (s, 3H), 1.81 (t, J = 7.1 Hz, 1H), 1.76 (t, J = 6.7 Hz, 1H), 0.54 (d, J = 3.4 Hz, 4H).	507.45
N-(4-(5-(4-(2-氮杂双环[3.1.0]己烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 7.7 Hz, 2H), 7.44 (s, 1H), 7.28 (t, J = 8.9 Hz, 3H), 5.95 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.96 (d, J = 12.2 Hz, 1H), 3.61 (s, 3H), 3.31-3.21 (s, 1H), 3.13 (d, J = 12.0 Hz, 1H), 2.06 (s, 1H), 1.95 (s, 4H), 1.60 (s, 1H), 0.77 (t, J = 6.5 Hz, 2H).	493.40
N-(4-(5-(4-((1R,4R)-2-氧杂-5-氮杂双环[2.2.2]辛烷-5-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (d, J = 2.7 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.59 - 7.25 (d, J = 7.8 Hz, 2H), 7.23 (dd, J = 8.3, 4.7 Hz, 4H), 6.25 - 5.72 (s, 3H), 5.53 (s, 1H), 4.06 (d, J = 17.0 Hz, 2H), 3.95 - 3.72 (dd, J = 18.0, 9.0 Hz, 3H), 3.65 (m, 3H), 3.51 (d, J = 3.7 Hz, 1H), 2.05 (d, J = 10.8 Hz, 2H), 1.95 (s, 3H), 1.85 - 1.64 (m, 2H).	523.35

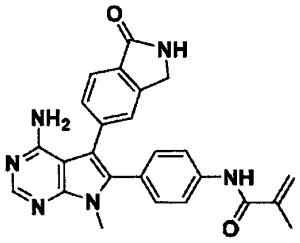
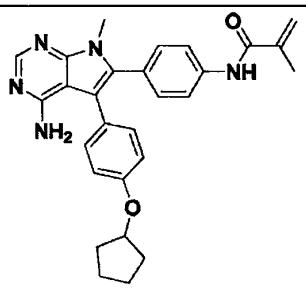
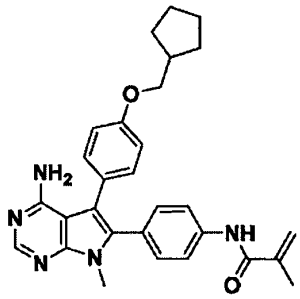
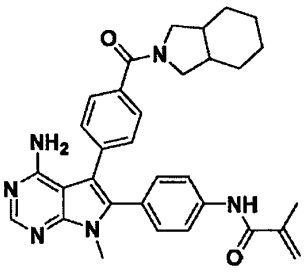
[0941]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(3-甲基哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.36 - 7.22 (m, 6H), 5.79 (s, 1H), 5.53 (s, 1H), 4.28 (s, 1H), 3.62 (s, 4H), 2.96 (s, 1H), 1.95 (s, 3H), 1.78 (d, J = 12.6 Hz, 1H), 1.57 (s, 2H), 1.42 (d, J = 13.0 Hz, 1H), 1.17 (t, J = 11.1 Hz, 1H), 0.77 (s, 3H).	509.40
N-(4-(4-氨基-7-甲基-5-(4-(4-甲基哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.3 Hz, 4H), 5.95 (s, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 4.42 (s, 1H), 3.61 (s, 4H), 2.99 (s, 1H), 2.72 (s, 1H), 1.95 (s, 3H), 1.62 (s, 3H), 1.14 - 1.07 (m, 1H), 1.05 (s, 1H), 0.92 (d, J = 6.2 Hz, 3H).	509.3
N-(4-(4-氨基-7-甲基-5-(4-(2-甲基哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 4H), 5.80 (s, 1H), 5.53 (s, 1H), 4.45 (s, 1H), 3.61 (s, 3H), 3.30 (s, 1H), 2.98 (s, 1H), 1.95 (s, 3H), 1.62 (dd, J = 19.7, 7.5 Hz, 5H), 1.36 (d, J = 12.8 Hz, 1H), 1.18 (d, J = 6.9 Hz, 3H).	509.4
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环丁基-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.32 - 7.23 (m, 6H), 5.97 (s, 0H), 5.79 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 4.32 (s, 1H), 3.62 (s, 3H), 2.93 (s, 3H), 2.22 (dq, J = 12.2, 9.4 Hz, 2H), 1.95 (s, 5H), 1.60 (s, 1H).	495.35

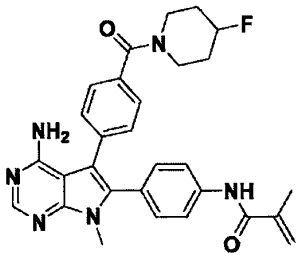
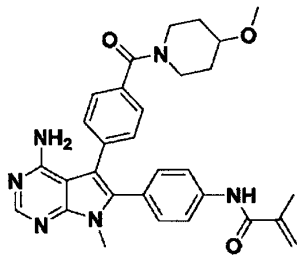
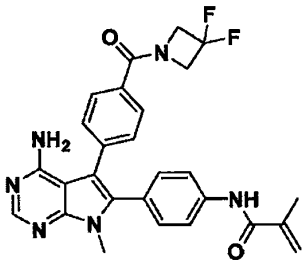
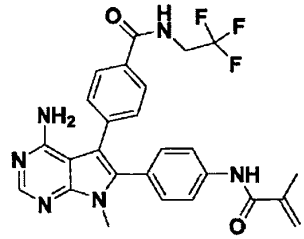
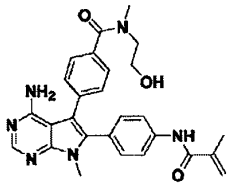
[0942]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环丁基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.59 (d, J = 7.6 Hz, 1H), 8.21 (s, 1H), 7.79 (d, J = 8.2 Hz, 2H), 7.73 - 7.67 (m, 2H), 7.32 - 7.23 (m, 4H), 5.92 (s, 2H), 5.79 (s, 1H), 5.54 (s, 1H), 4.40 (q, J = 8.2 Hz, 1H), 3.61 (s, 3H), 2.20 (d, J = 8.7 Hz, 3H), 2.12 - 1.98 (m, 2H), 1.95 (d, J = 1.4 Hz, 3H), 1.65 (td, J = 10.7, 9.4, 6.1 Hz, 2H).	481.35
N-(4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)环丁烷甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.76 (s, 1H), 8.18 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 5.79 (s, 1H), 5.58 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 3.26 - 3.17 (m, 1H), 2.22 (t, J = 9.5 Hz, 2H), 2.10 (d, J = 9.3 Hz, 2H), 1.95 (s, 4H), 1.80 (d, J = 10.6 Hz, 1H).	481.20
N-(4-(5-(4-(5-氮杂螺[2.5]辛烷-5-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.26 (s, 6H), 5.79 (s, 2H), 5.53 (s, 1H), 3.62 (s, 3H), 3.39 (s, 2H), 3.30 (s, 1H), 3.09 (s, 1H), 1.95 (s, 3H), 1.60 (s, 2H), 1.46 (s, 2H), 0.46 (s, 1H), 0.29 (s, 2H), 0.11 (s, 1H).	521.40
N-(4-(5-(4-(6-氮杂螺[2.5]辛烷-6-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.26 (dd, J = 8.4, 2.6 Hz, 4H), 6.25 - 5.75 (s, 2H), 5.53 (s, 1H), 3.85 - 3.35 (s, 7H), 1.95 (s, 3H), 1.35 (s, 4H), 0.35 (s, 4H).	521.4

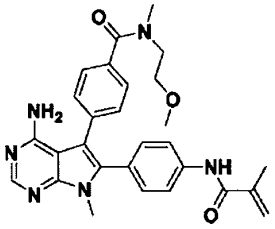
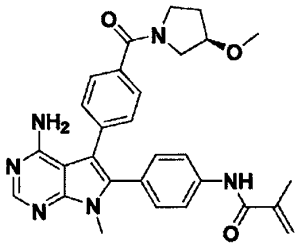
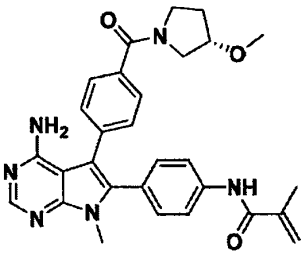
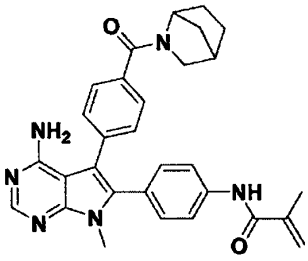
[0943]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-侧氧基异吲哚啉-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.51 (s, 1H), 8.21 (s, 1H), 7.73 - 7.66 (m, 2H), 7.59 (d, J = 7.7 Hz, 1H), 7.43 (s, 1H), 7.35 - 7.23 (m, 3H), 5.91 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 4.33 (s, 2H), 3.62 (s, 3H), 1.95 (s, 3H).	439.25
N-(4-(4-氨基-5-(4-(环戊基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.17 (s, 1H), 7.73 - 7.66 (m, 2H), 7.30 - 7.23 (m, 2H), 7.18 - 7.09 (m, 2H), 6.92 - 6.83 (m, 2H), 5.80 (s, 1H), 5.53 (d, J = 1.9 Hz, 1H), 4.79 (td, J = 6.0, 3.0 Hz, 1H), 3.60 (s, 3H), 1.97 - 1.86 (m, 5H), 1.75 - 1.65 (m, 4H), 1.58 (q, J = 6.0, 3.6 Hz, 2H).	468.30
N-(4-(4-氨基-5-(4-(环戊基甲氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.17 (s, 1H), 7.72 - 7.66 (m, 2H), 7.29 - 7.23 (m, 2H), 7.17 - 7.10 (m, 2H), 6.94 - 6.87 (m, 2H), 5.79 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.83 (d, J = 6.9 Hz, 2H), 3.60 (s, 3H), 2.28 (dq, J = 14.7, 7.4 Hz, 1H), 2.08 (s, 1H), 1.95 (t, J = 1.2 Hz, 3H), 1.76 (ddd, J = 11.9, 9.2, 4.7 Hz, 2H), 1.65 - 1.47 (m, 4H), 1.39 - 1.26 (m, 2H).	482.35
N-(4-(4-氨基-7-甲基-5-(4-(十氢-1H-异吲哚-2-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.37 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 4H), 6.74 (s, 3H), 5.80 (s, 1H), 5.54 (s, 1H), 3.66 (s, 3H), 3.51 - 3.41 (m, 2H), 3.39 - 3.26 (m, 1H), 3.31 (s, 1H), 2.25 (d, J = 6.9 Hz, 1H), 2.16 (s, 1H), 1.95 (s, 3H), 1.49 (d, J = 9.3 Hz, 5H), 1.33 - 1.26 (m, 3H).	535.50

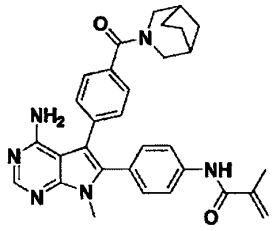
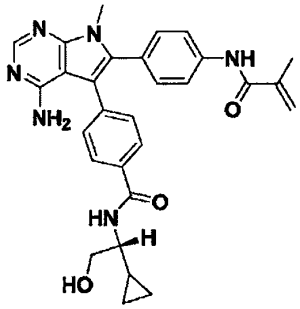
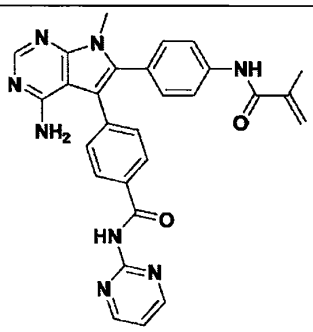
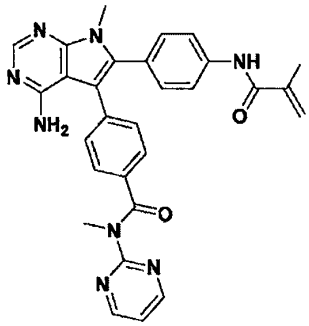
[0944]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-(4-氟哌啶-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.29 (s, 1H), 7.75 - 7.68 (m, 2H), 7.41 - 7.34 (m, 2H), 7.27 (dd, J = 8.4, 2.4 Hz, 4H), 5.80 (s, 1H), 5.54 (s, 1H), 4.97 (s, 1H), 4.85 (s, 1H), 3.63 (s, 3H), 3.61 (s, 3H), 1.95 (s, 3H), 1.73 (s, 3H).	513.40
N-(4-(4-氨基-5-(4-(4-甲氧基哌啶-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.74 - 7.67 (m, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.26 (d, J = 8.1 Hz, 4H), 5.96 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.89 (s, 1H), 3.61 (s, 3H), 1.95 (s, 3H), 1.84 (s, 2H), 1.44 (s, 2H).	525.45
N-(4-(4-氨基-5-(4-(3,3-二氟氮杂环丁烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.75 - 7.63 (m, 4H), 7.34 - 7.23 (m, 4H), 5.96 (s, 1H), 5.80 (t, J = 1.0 Hz, 1H), 5.54 (t, J = 1.4 Hz, 1H), 4.78 (s, 2H), 4.52 (s, 2H), 3.61 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	503.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.09 (t, J = 6.3 Hz, 1H), 8.36 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.76 - 7.68 (m, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.30 - 7.24 (m, 2H), 6.69 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 4.08 (td, J = 9.9, 6.3 Hz, 2H), 3.65 (s, 3H), 1.95 (s, 3H).	509.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-羟乙基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.30 - 7.23 (m, 4H), 5.94 (s, 0H), 5.80 (s, 1H), 5.53 (s, 1H), 4.77 (s, 1H), 3.62 (s, 4H), 3.50 (s, 2H), 3.32 (s, 1H), 2.98 (s, 3H), 1.95 (s, 3H), 1.25 (s, 1H).	485.35

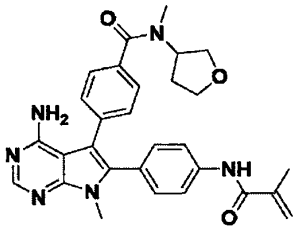
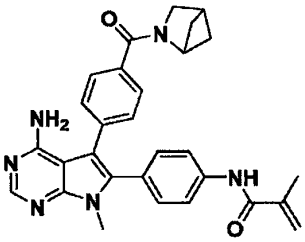
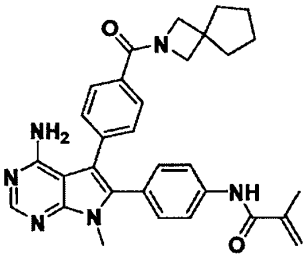
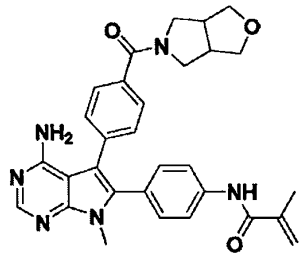
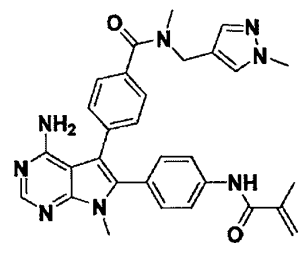
[0945]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基乙基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.73 - 7.67 (m, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.2 Hz, 4H), 5.80 (s, 2H), 5.53 (s, 1H), 3.62 (s, 3H), 3.41 (s, 2H), 3.29 (s, 1H), 3.11 (s, 2H), 2.97 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H).	499.40
(R)-N-(4-(4-氨基-5-(4-(3-甲氧基吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.52 (dd, J = 8.2, 2.1 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.31 - 7.24 (m, 2H), 5.85 (s, 1H), 5.54 (d, J = 2.1 Hz, 1H),4.20 - 4.00 (dq, J = 4.2, 2.3 Hz, 1H), 3.75 (s, 4H), 3.55 (s, 3H), 3.35 (dd, J = 7.7, 4.6 Hz, 2H), 3.25(m, 2H), 2.31 - 1.89 (m, 5H).	511.4
(S)-N-(4-(4-氨基-5-(4-(3-甲氧基吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.74 - 7.66 (m, 2H), 7.48 (dd, J = 7.9, 5.6 Hz, 2H), 7.26 (dd, J = 8.2, 1.7 Hz, 4H), 5.93 (s, 1H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.97 (d, J = 32.6 Hz, 1H), 3.61 (s, 3H), 3.51 (d, J = 11.3 Hz, 3H), 3.26 (s, 2H), 3.17 (s, 2H), 2.01 - 1.92 (m, 5H).	511.45
N-(4-(5-(4-(2-氮杂双环[2.2.1]庚烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (d, J = 1.7 Hz, 1H), 7.68 (dd, J = 8.7, 2.4 Hz, 2H), 7.50 (dd, J = 8.3, 2.8 Hz, 2H), 7.39 (dd, J = 11.2, 8.1 Hz, 2H), 7.29 (dq, J = 8.6, 2.1 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 4.18 (s, 1H), 3.71 (d, J = 1.8 Hz, 3H), 3.55 (d, J = 11.3 Hz, 1H), 3.19 (dd, J = 11.3, 1.7 Hz, 1H), 2.70 (s, 1H), 2.08 - 2.02 (m, 3H), 1.80 (q, J = 12.8, 10.8 Hz, 3H), 1.70 (d, J = 10.3 Hz, 1H), 1.59 (s, 1H), 1.52 (d, J = 9.7 Hz, 1H).	507.40

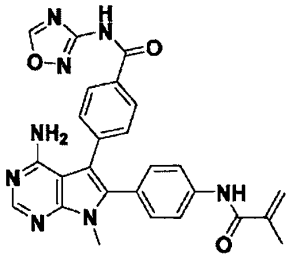
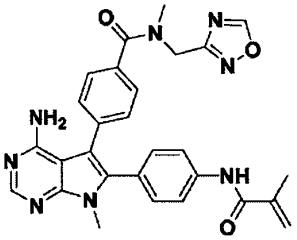
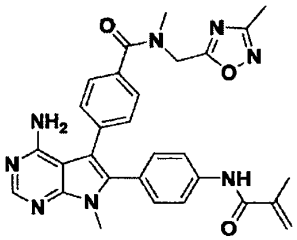
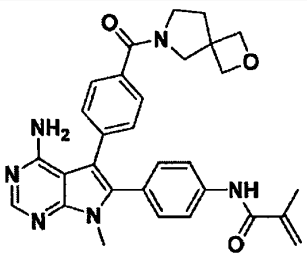
[0946]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-(4-(3-氮杂-双环[3.2.1]辛烷-3-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.74 - 7.67 (m, 2H), 7.28 (q, J = 8.1 Hz, 6H), 5.94 (s, 2H), 5.80 (s, 1H), 5.53 (d, J = 2.0 Hz, 1H), 4.29 (s, 1H), 3.38 (s, 1H), 3.32 (s, 2H), 3.17 (s, 1H), 2.79 (s, 1H), 2.28 - 2.19 (m, 2H), 2.12 (s, 1H), 1.95 (d, J = 1.4 Hz, 3H), 1.60 (d, J = 10.5 Hz, 3H), 1.49 (s, 3H), 1.39 (s, 1H).	521.40
(R)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1-环丙基-2-羟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.32 - 7.23 (m, 4H), 5.79 (s, 2H), 5.53 (s, 1H), 4.63 (t, J = 5.7 Hz, 1H), 3.62 (s, 3H), 3.58 - 3.39 (m, 3H), 1.95 (s, 3H), 0.98 (d, J = 8.1 Hz, 1H), 0.48 - 0.42 (m, 1H), 0.38 - 0.13 (m, 3H).	511.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(嘧啶-2-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.73 (d, J = 4.8 Hz, 2H), 8.22 (s, 1H), 7.96 - 7.89 (m, 2H), 7.77 - 7.69 (m, 2H), 7.38 - 7.30 (m, 2H), 7.33 - 7.22 (m, 3H), 5.98 (s, 1H), 5.80 (t, J = 1.0 Hz, 1H), 5.53 (t, J = 1.4 Hz, 1H), 3.62 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	505.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-(嘧啶-2-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.52 (d, J = 4.8 Hz, 2H), 8.19 (s, 1H), 7.75 - 7.68 (m, 2H), 7.25 - 7.08 (m, 7H), 5.82 (d, J = 1.3 Hz, 2H), 5.56 (t, J = 1.4 Hz, 1H), 3.61 (s, 3H), 3.54 (s, 3H), 1.97 (d, J = 1.3 Hz, 3H), 1.24 (s, 1H).	519.25

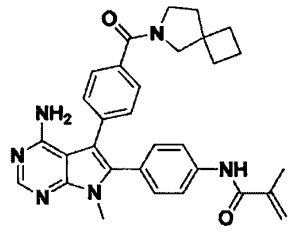
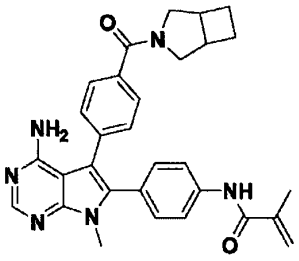
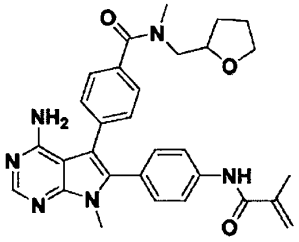
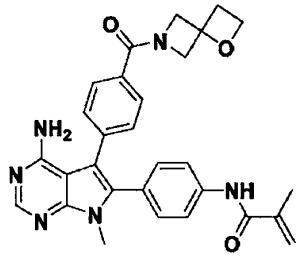
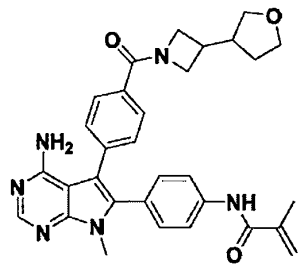
[0947]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.40 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.35 (s, 2H), 7.30 - 7.23 (m, 4H), 5.80 (s, 1H), 5.54 (s, 1H), 3.99 - 3.89 (m, 1H), 3.78 (dd, J = 9.6, 3.9 Hz, 1H), 3.67 (s, 3H), 3.42 (s, 1H), 2.87 (s, 3H), 2.11 (s, 1H), 1.95 (s, 3H).	511.40
N-(4-(5-(4-(2-氮杂双环[2.1.1]己烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.75 - 7.67 (m, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.27 (d, J = 8.0 Hz, 4H), 5.95 (s, 1H), 5.80 (t, J = 1.0 Hz, 1H), 5.53 (t, J = 1.5 Hz, 1H), 4.69 - 4.33 (d, J = 6.8 Hz, 1H), 3.61 (s, 3H), 3.45 (d, J = 9.0 Hz, 2H), 2.93 - 2.84 (m, 1H), 1.95 (d, J = 1.2 Hz, 4H), 1.47 (s, 1H), 1.33 (s, 1H).	493.25
N-(4-(5-(4-(2-氮杂螺[3.4]辛烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.66 (dd, J = 10.2, 8.2 Hz, 4H), 7.42 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 4.22 (s, 2H), 4.02 (s, 2H), 3.70 (s, 3H), 2.05 (d, J = 4.9 Hz, 3H), 1.87 (d, J = 6.6 Hz, 4H), 1.68 - 1.64 (m, 4H).	521.4
N-(4-(4-氨基-5-(4-(六氢-1H-呋喃并[3,4-c]吡咯-5-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.69 (m, 2H), 7.55 (m, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.25 (m, 2H), 5.81 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 4.05 - 3.72 (s, 4H), 3.70 (s, 5H), 3.55 (s, 1H), 3.42 (d, J = 11.6 Hz, 1H), 3.03 (s, 2H), 2.04 (d, J = 1.6 Hz, 3H).	523.4
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((1-甲基-1H-吡唑-4-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.58 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.26 (dd, J = 8.1, 3.7 Hz, 4H), 5.80 (s, 2H), 5.56 - 5.51 (m, 1H), 4.44 (s, 1H), 4.28 (s, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 2.87 (s, 3H), 1.95 (s, 3H).	535.45

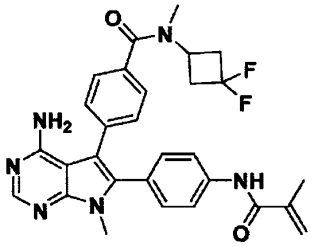
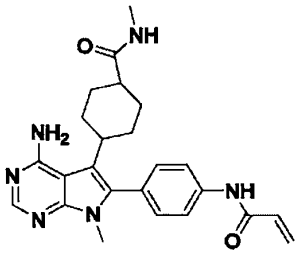
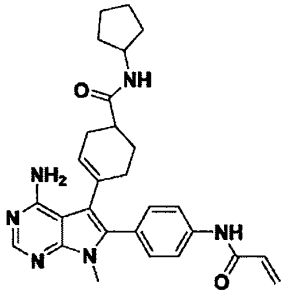
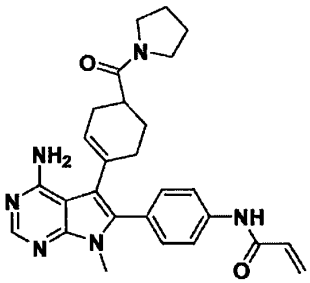
[0948]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1,2,4-恶二唑-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 9.91 (s, 1H), 9.01 (s, 1H), 8.23 (s, 1H), 8.07 - 8.00 (m, 2H), 7.76 - 7.68 (m, 2H), 7.47 - 7.40 (m, 2H), 7.32 - 7.25 (m, 2H), 6.04 (s, 2H), 5.80 (s, 1H), 5.54 (d, J = 1.7 Hz, 1H), 3.62 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	495.2
N-((1,2,4-恶二唑-3-基)甲基)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.62 (s, 1H), 8.20 (d, J = 2.6 Hz, 1H), 7.73 - 7.67 (m, 2H), 7.44 - 7.37 (m, 2H), 7.26 (d, J = 8.5 Hz, 4H), 5.97 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 4.85 (s, 1H), 4.73 (s, 1H), 3.32 (s, 3H), 3.05 (s, 1H), 2.98 (s, 1H), 1.95 (t, J = 1.3 Hz, 3H).	523.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((3-甲基-1,2,4-恶二唑-5-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.42 (s, 2H), 7.26 (d, J = 8.4 Hz, 3H), 5.80 (s, 1H), 5.53 (s, 1H), 4.91 (s, 2H), 3.61 (s, 3H), 3.29 (s, 1H), 3.11 (s, 3H), 2.35 (s, 3H), 1.95 (s, 3H).	537.45
N-(4-(5-(4-(2-氧杂-6-氮杂螺[3.4]辛烷-6-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.71 (dd, J = 8.7, 3.5 Hz, 2H), 7.49 (t, J = 7.0 Hz, 2H), 7.27 (t, J = 7.5 Hz, 4H), 5.96 (s, 1H), 5.80 (t, J = 1.0 Hz, 1H), 5.56 - 5.51 (m, 1H), 4.62 (d, J = 6.0 Hz, 1H), 4.47 (q, J = 7.7, 6.8 Hz, 3H), 3.70 (s, 2H), 3.61 (s, 3H), 3.46 (q, J = 7.3 Hz, 2H), 2.14 (dt, J = 12.1, 7.0 Hz, 2H), 1.95 (t, J = 1.2 Hz, 3H).	523.25

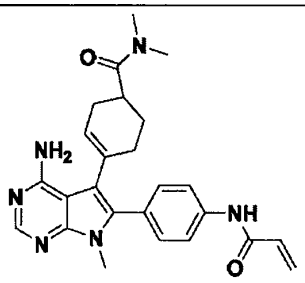
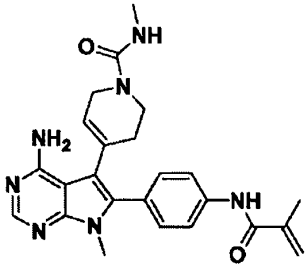
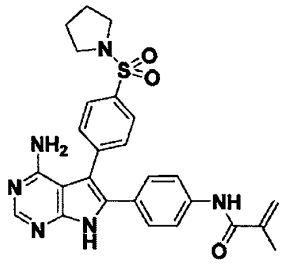
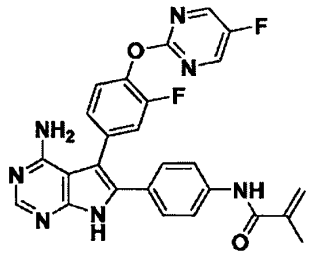
[0949]

化合物	结构	质子 NMR	MS [M+1]
N-{4-[4-氨基-5-(4-{6-氮杂螺[3.4]辛烷-6-羰基}苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.38 (s, 1H), 7.73 (dd, J = 8.7, 2.7 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.31 - 7.23 (m, 4H), 6.80 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.43 (dd, J = 11.9, 5.6 Hz, 5H), 2.03 (s, 1H), 1.95 (s, 3H), 1.89 (dd, J = 18.8, 5.4 Hz, 8H).	521.45
N-(4-(5-(4-(3-氮杂双环[3.2.0]庚烷-3-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.52 - 7.45 (m, 2H), 7.31 - 7.23 (m, 4H), 5.80 (s, 2H), 5.53 (t, J = 1.4 Hz, 1H), 3.96 (s, 1H), 3.61 (s, 3H), 3.32 (s, 5H), 2.91 (s, 2H), 2.14 (s, 2H), 1.95 (d, J = 1.2 Hz, 3H), 1.60 (s, 2H).	507.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((四氢呋喃-2-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.33 (s, 2H), 7.26 (dd, J = 8.5, 2.9 Hz, 4H), 5.79 (s, 1H), 5.56 - 5.50 (m, 1H), 4.09 (s, 1H), 4.03 (s, 1H), 3.79 (s, 1H), 3.62 (s, 3H), 2.99 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H), 1.54 (s, 1H).	525.45
N-{4-[4-氨基-7-甲基-5-(4-{1-氧杂-6-氮杂螺[3.3]庚烷-6-羰基}苯基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.31 - 7.23 (m, 4H), 5.91 (s, 3H), 5.80 (s, 1H), 5.54 (s, 1H), 4.53 (s, 1H), 4.40 (t, J = 7.5 Hz, 2H), 4.31 (s, 1H), 4.12 (s, 1H), 3.61 (s, 3H), 2.83 (t, J = 7.4 Hz, 2H), 1.95 (s, 3H).	509.35
N-(4-(4-氨基-7-甲基-5-(4-(3-(四氢呋喃-3-基)氮杂环丁烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.27 (t, J = 8.6 Hz, 4H), 5.93 (s, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 4.39 (d, J = 8.1 Hz, 1H), 4.20 - 3.90 (m, 2H), 3.73 (d, J = 7.4 Hz, 3H), 3.61 (s, 4H), 3.30 (s, 2H), 2.59 (s, 1H), 1.95 (s, 4H), 1.45 (s, 1H).	537.35

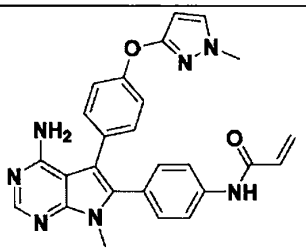
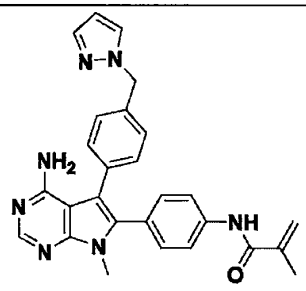
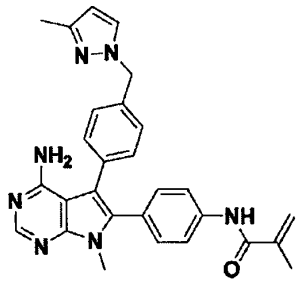
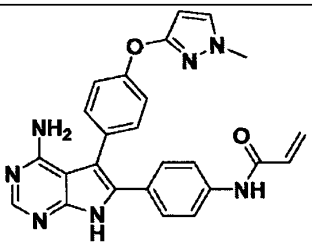
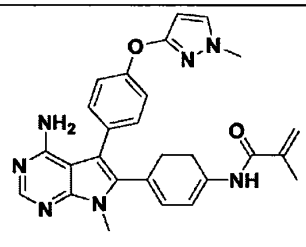
[0950]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3,3-二氟环丁基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.37 (d, J = 7.7 Hz, 2H), 7.31 - 7.23 (m, 4H), 6.05 (s, 2H), 5.80 (s, 1H), 5.53 (d, J = 1.9 Hz, 1H), 4.45 (s, 1H), 3.62 (s, 3H), 3.01 - 2.69 (m, 7H), 1.95 (d, J = 1.5 Hz, 3H).	531.40
4-(6-(4-乙酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基环己烷-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.07 (s, 1H), 7.89 (d, J = 4.4 Hz, 1H), 7.85 - 7.79 (m, 2H), 7.39 - 7.32 (m, 2H), 6.93 (s, 2H), 6.49 (dd, J = 17.0, 10.1 Hz, 1H), 6.31 (dd, J = 17.0, 2.0 Hz, 1H), 5.80 (dd, J = 10.0, 2.0 Hz, 1H), 3.43 (s, 3H), 2.60 (d, J = 4.6 Hz, 4H), 2.45 (s, 1H), 2.21 - 2.10 (m, 2H), 1.83 (d, J = 12.9 Hz, 2H), 1.52 - 1.39 (m, 4H).	433.35
4-(6-(4-乙酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环戊基环己-3-烯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.10 (s, 1H), 7.78 (dd, J = 8.2, 6.6 Hz, 3H), 7.48 - 7.40 (m, 2H), 6.47 (dd, J = 17.0, 10.1 Hz, 1H), 6.30 (dd, J = 17.0, 2.1 Hz, 1H), 5.83 - 5.75 (m, 2H), 3.99 (p, J = 6.8 Hz, 1H), 3.57 (s, 3H), 2.45 (t, J = 6.0 Hz, 1H), 2.28 (s, 1H), 2.19 (d, J = 17.9 Hz, 1H), 1.90 - 1.84 (m, 2H), 1.82 - 1.69 (m, 2H), 1.62 (s, 4H), 1.47 (q, J = 7.0 Hz, 2H), 1.35 (s, 1H), 1.32 (s, 1H).	485.2
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.10 (s, 1H), 7.82 - 7.75 (m, 2H), 7.49 - 7.42 (m, 2H), 6.47 (dd, J = 17.0, 10.1 Hz, 1H), 6.30 (dd, J = 17.0, 2.1 Hz, 1H), 5.83 - 5.73 (m, 2H), 3.58 (s, 3H), 3.51 (dt, J = 10.0, 6.6 Hz, 1H), 3.43 (dt, J = 10.0, 6.7 Hz, 1H), 3.32 - 3.20 (m, 2H), 2.82 (q, J = 6.0 Hz, 1H), 2.27 (d, J = 12.9 Hz, 2H), 1.89 (s, 4H), 1.76 (p, J = 6.7 Hz, 2H), 1.63 (d, J = 6.1 Hz, 2H).	471.2

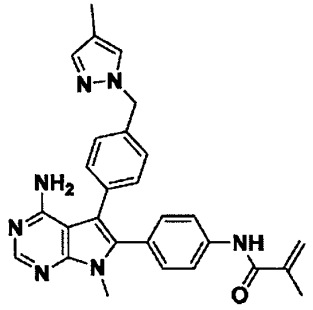
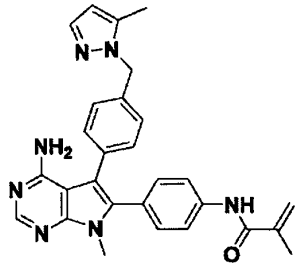
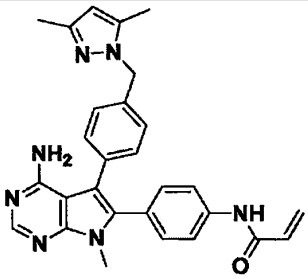
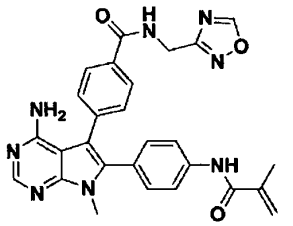
[0951]

化合物	结构	质子 NMR	MS [M+1]
4-(6-(4-乙酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N,N-二甲基环己-3-烯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.10 (s, 1H), 7.82 - 7.75 (m, 2H), 7.49 - 7.41 (m, 2H), 6.47 (dd, J = 17.0, 10.1 Hz, 1H), 6.29 (dd, J = 17.0, 2.1 Hz, 1H), 5.83 - 5.73 (m, 2H), 3.58 (s, 3H), 3.02 (s, 3H), 3.08 - 2.97 (m, 1H), 2.82 (s, 3H), 2.27 (d, J = 12.9 Hz, 2H), 1.90 (s, 1H), 1.83 (d, J = 17.4 Hz, 1H), 1.61 (d, J = 6.0 Hz, 2H).	445.2
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-5,6-二氢吡啶-1(2H)-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.13 (s, 1H), 7.84 - 7.78 (m, 2H), 7.44 - 7.38 (m, 2H), 6.34 (d, J = 4.5 Hz, 1H), 6.25 (s, 2H), 5.83 (s, 1H), 5.78 (s, 1H), 5.55 (d, J = 1.8 Hz, 1H), 3.91 (d, J = 3.3 Hz, 2H), 3.56 (s, 3H), 2.57 (d, J = 4.3 Hz, 3H), 1.97 (d, J = 1.4 Hz, 3H), 1.95 (s, 2H).	446.35
N-(4-(4-氨基-5-(4-(吡咯烷-1-基磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 9.85 (s, 1H), 8.14 (s, 1H), 7.88 - 7.81 (m, 2H), 7.62 - 7.52 (m, 4H), 7.16 (d, J = 8.8 Hz, 2H), 5.86 (s, 2H), 5.78 (s, 1H), 5.52 (s, 1H), 3.24 - 3.12 (m, 2H), 1.94 (d, J = 1.2 Hz, 3H), 1.71 - 1.63 (m, 3H), 1.57 (s, 1H), 1.32 (q, J = 7.2 Hz, 1H), 0.94 (t, J = 7.2 Hz, 1H).	503.15
N-(4-(4-氨基-5-(3-氟-4-((5-氟嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 12.14 (s, 1H), 9.85 (s, 1H), 8.81 (s, 2H), 8.14 (s, 1H), 7.68 - 7.61 (m, 2H), 7.48 (t, J = 8.4 Hz, 1H), 7.38 - 7.27 (m, 3H), 7.24 (dd, J = 8.3, 2.0 Hz, 1H), 5.80 (s, 1H), 5.75 (s, 1H), 5.53 (d, J = 1.6 Hz, 1H), 1.95 (s, 3H).	500.35

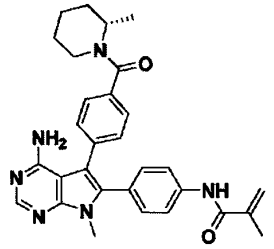
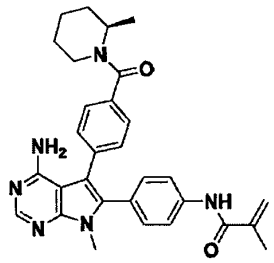
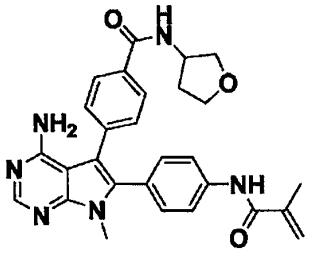
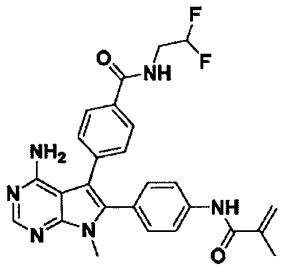
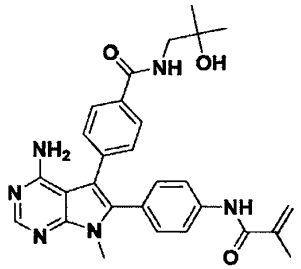
[0952]

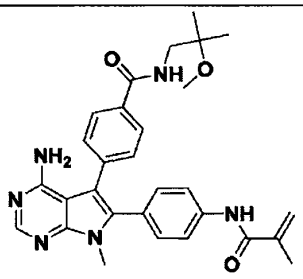
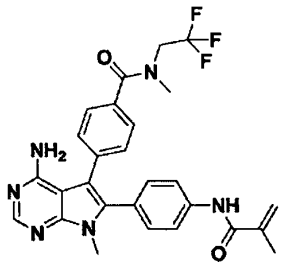
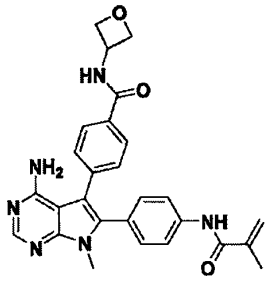
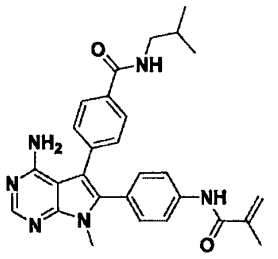
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.18 (s, 1H), 7.72 - 7.62 (m, 3H), 7.32 - 7.25 (m, 2H), 7.25 - 7.16 (m, 2H), 7.07 - 6.98 (m, 2H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.88 (d, J = 2.3 Hz, 1H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.75 (s, 3H), 3.60 (s, 3H).	466.30
N-(4-(5-(4-((1H-吡唑-1-基)甲基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.19 (s, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.72 - 7.64 (m, 2H), 7.48 (d, J = 1.8 Hz, 1H), 7.31 - 7.20 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 6.28 (t, J = 2.0 Hz, 1H), 5.80 (s, 2H), 5.53 (t, J = 1.6 Hz, 1H), 5.35 (s, 2H), 3.59 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	464.30
N-(4-(4-氨基-7-甲基-5-(4-((3-甲基-1H-吡唑-1-基)甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.19 (s, 1H), 7.69 (dd, J = 5.4, 3.1 Hz, 3H), 7.30 - 7.18 (m, 4H), 7.14 (d, J = 8.2 Hz, 2H), 6.04 (d, J = 2.2 Hz, 1H), 5.91 (s, 2H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 5.24 (s, 2H), 3.59 (s, 3H), 2.15 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	478.35
N-(4-(4-氨基-5-(4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.13 (s, 1H), 8.12 (d, J = 13.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.59 - 7.52 (m, 2H), 7.46 - 7.39 (m, 2H), 7.23 - 7.14 (m, 3H), 6.57 - 6.37 (m, 1H), 6.31-6.11 (m, 1H), 5.96 (s, 2H), 5.81 - 5.69 (m, 1H), 3.80 (s, 3H).	452.15
N-(4-(4-氨基-7-甲基-5-(4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.18 (s, 1H), 7.74 - 7.67 (m, 2H), 7.65 (d, J = 2.3 Hz, 1H), 7.31 - 7.23 (m, 2H), 7.23 - 7.16 (m, 2H), 7.06 - 6.98 (m, 2H), 5.88 (d, J = 2.3 Hz, 1H), 5.85 - 5.77 (m, 3H), 5.56 - 5.51 (m, 1H), 3.75 (s, 3H), 3.60 (s, 3H), 1.95 (d, J = 1.1 Hz, 3H).	480.35

[0953]

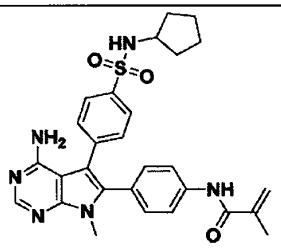
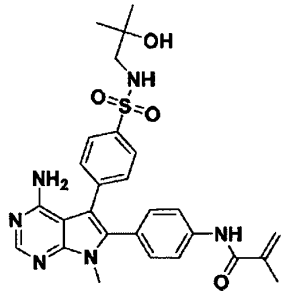
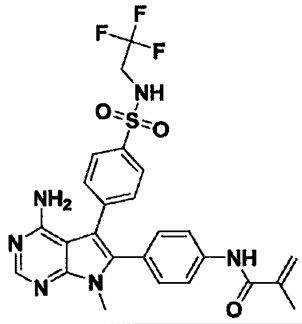
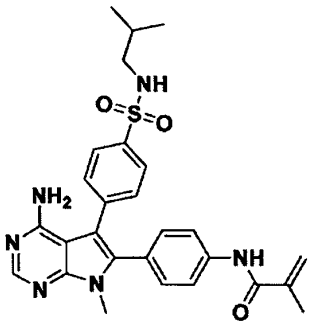
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基-1H-吡唑-1-基)甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.88 (s, 1H), 8.19 (s, 1H), 7.72 - 7.65 (m, 2H), 7.58 (s, 1H), 7.27 (s, 2H), 7.27 - 7.17 (m, 3H), 7.13 (d, J = 8.1 Hz, 2H), 5.80 (s, 1H), 5.71 (s, 1H), 5.56 - 5.51 (m, 1H), 5.25 (s, 2H), 3.59 (s, 3H), 2.01 (s, 3H), 1.95 (d, J = 1.1 Hz, 3H).	478.35
N-(4-(4-氨基-7-甲基-5-(4-((5-甲基-1H-吡唑-1-基)甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.18 (s, 1H), 7.72 - 7.64 (m, 2H), 7.35 (d, J = 1.7 Hz, 1H), 7.29 - 7.17 (m, 4H), 7.04 (d, J = 7.9 Hz, 2H), 6.07 (d, J = 1.9 Hz, 1H), 5.96 (s, 1H), 5.80 (s, 1H), 5.78 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 5.30 (s, 2H), 3.59 (s, 3H), 2.21 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	478.35
N-(4-(4-氨基-5-(4-((3,5-二甲基-1H-吡唑-1-基)甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.24 (s, 1H), 8.18 (s, 1H), 7.70 - 7.63 (m, 2H), 7.30 - 7.21 (m, 2H), 7.24 - 7.16 (m, 2H), 7.04 (d, J = 8.1 Hz, 2H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.95 (s, 2H), 5.85 (s, 1H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 5.19 (s, 2H), 3.59 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H).	478.40
N-((1,2,4-恶二唑-3-基)甲基)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.55 (s, 1H), 9.16 (t, *J* = 5.8 Hz, 1H), 8.21 (s, 1H), 7.86 - 7.79 (m, 2H), 7.74 - 7.66 (m, 2H), 7.36 - 7.29 (m, 2H), 7.29 - 7.22 (m, 2H), 5.92 (s, 1H), 5.80 (s, 1H), 5.53 (t, *J* = 1.5 Hz, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 3.32 (s, 3H), 1.95 (d, *J* = 1.3 Hz, 3H).	509.30

[0954]

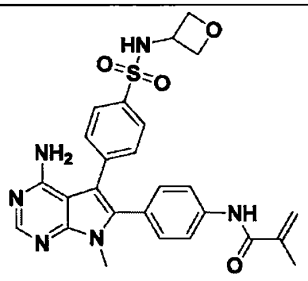
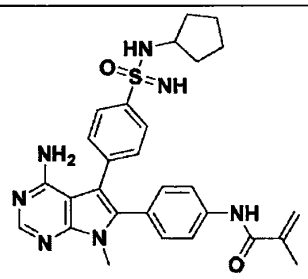
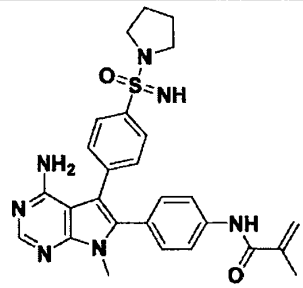
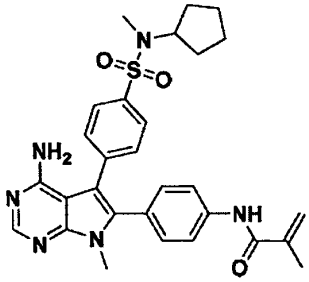
化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(4-(2-甲基哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.34 - 7.22 (m, 6H), 5.79 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H), 1.61 (d, J = 16.0 Hz, 3H), 1.50 (s, 2H), 1.36 (d, J = 12.6 Hz, 1H), 1.18 (d, J = 7.0 Hz, 3H).	509.45
(R)-N-(4-(4-氨基-7-甲基-5-(4-(2-甲基哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.34 - 7.22 (m, 6H), 5.79 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 2.98 (s, 1H), 1.95 (d, J = 1.3 Hz, 3H), 1.63 (s, 1H), 1.59 (s, 2H), 1.51 (s, 1H), 1.37 (s, 1H), 1.18 (d, J = 6.9 Hz, 3H).	509.45
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.51 (d, J = 6.5 Hz, 1H), 8.21 (s, 1H), 7.84 - 7.78 (m, 2H), 7.74 - 7.66 (m, 2H), 7.32 - 7.22 (m, 4H), 5.91 (s, 1H), 5.79 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 4.44 (d, J = 8.0 Hz, 1H), 3.84 (td, J = 8.7, 6.7 Hz, 2H), 3.71 (td, J = 8.1, 5.7 Hz, 1H), 3.61 (s, 3H), 3.57 (dd, J = 8.9, 4.4 Hz, 1H), 2.20 - 2.06 (m, 1H), 1.97 - 1.85 (m, 4H).	497.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2,2-二氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.84 (t, J = 5.9 Hz, 1H), 8.21 (s, 1H), 7.83 (d, J = 7.9 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 6.33 - 5.63 (m, 4H), 5.53 (s, 1H), 3.72 - 3.61 (m, 3H), 3.32 (s, 2H), 1.95 (s, 3H).	491.15
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-羟基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (d, J = 9.3 Hz, 2H), 7.85 - 7.79 (m, 2H), 7.74 - 7.66 (m, 2H), 7.33 - 7.23 (m, 4H), 5.92 (s, 1H), 5.80 (s, 1H), 5.56 - 5.51 (m, 1H), 4.53 (s, 1H), 3.61 (s, 3H), 3.24 (d, J = 6.1 Hz, 2H), 1.95 (d, J = 1.2 Hz, 3H), 1.10 (s, 6H).	499.40

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (d, J = 5.4 Hz, 2H), 7.84 - 7.77 (m, 2H), 7.74 - 7.67 (m, 2H), 7.33 - 7.24 (m, 4H), 5.90 (s, 1H), 5.80 (s, 1H), 5.53 (d, J = 1.9 Hz, 1H), 3.61 (s, 3H), 3.32 (d, J = 6.5 Hz, 1H), 3.15 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H), 1.11 (s, 6H).	513.50
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-(2,2,2-三氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.39 (s, 2H), 7.27 (dd, J = 13.3, 8.2 Hz, 4H), 5.98 (s, 2H), 5.80 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 3.32 (s, 2H), 3.07 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	523.40
[0955] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(氧杂环丁-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.08 (d, J = 6.4 Hz, 1H), 8.21 (s, 1H), 7.86 - 7.80 (m, 2H), 7.75 - 7.67 (m, 2H), 7.35 - 7.22 (m, 4H), 5.92-5.79 (s, 2H), 5.54 (t, J = 1.5 Hz, 1H), 4.99 (h, J = 6.9 Hz, 1H), 4.76 (dd, J = 7.5, 6.3 Hz, 2H), 4.58 (t, J = 6.4 Hz, 2H), 3.61 (s, 3H), 1.95 (d, J = 1.1 Hz, 3H).	483.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-异丁基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.43 (t, J = 5.8 Hz, 1H), 8.21 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.28 (dd, J = 11.2, 8.4 Hz, 4H), 5.79 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 3.07 (t, J = 6.4 Hz, 2H), 1.95 (d, J = 1.2 Hz, 3H), 1.83 (dt, J = 13.6, 6.8 Hz, 1H), 0.89 (d, J = 6.7 Hz, 6H).	483.40

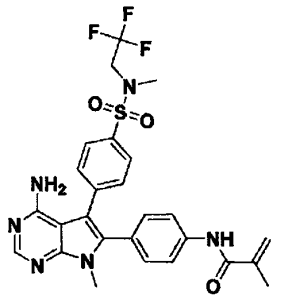
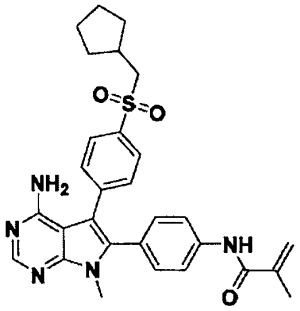
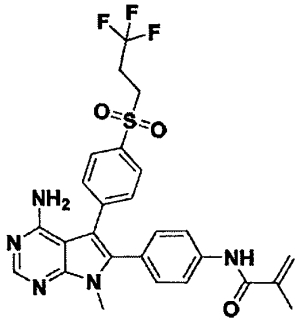
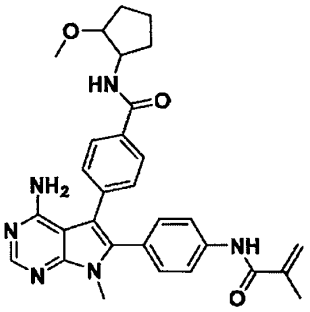
[0956]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-(N-环戊基胺磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.77 - 7.66 (m, 4H), 7.57 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 5.96 (s, 0H), 5.78 (s, 1H), 5.53 (s, 1H), 3.63 (s, 3H), 3.42 (q, J = 7.0 Hz, 1H), 3.32 (s, 1H), 1.94 (s, 3H), 1.53 (s, 3H), 1.37 (s, 2H), 1.21 (d, J = 6.0 Hz, 2H).	531.35
N-(4-(4-氨基-5-(4-(N-(2-羟基-2-甲基丙基)胺磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.73 (t, J = 8.3 Hz, 4H), 7.45 (t, J = 6.5 Hz, 1H), 7.42 - 7.36 (m, 2H), 7.29 - 7.21 (m, 2H), 5.80 (s, 1H), 5.53 (t, J = 1.6 Hz, 1H), 4.38 (s, 1H), 3.61 (s, 3H), 3.32 (s, 2H), 2.66 (d, J = 6.5 Hz, 2H), 1.95 (t, J = 1.3 Hz, 3H), 1.03 (s, 6H).	535.40
N-(4-(4-氨基-7-甲基-5-(4-(N-(2,2,2-三氟乙基)胺磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.59 (s, 1H), 8.22 (s, 1H), 7.80 - 7.68 (m, 4H), 7.40 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 5.99 (s, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.74 (d, J = 9.4 Hz, 2H), 3.69 (d, J = 9.5 Hz, 1H), 3.53 (s, 3H), 1.95 (s, 3H).	545.30
N-(4-(4-氨基-5-(4-(N-异丁基胺磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.75 - 7.68 (m, 4H), 7.55 (t, J = 6.1 Hz, 1H), 7.42 - 7.35 (m, 2H), 7.27 - 7.20 (m, 2H), 5.95 (s, 2H), 5.79 (d, J = 1.3 Hz, 1H), 5.56 - 5.51 (m, 1H), 3.62 (s, 3H), 2.58 (t, J = 6.4 Hz, 2H), 1.95 (t, J = 1.3 Hz, 3H), 1.58 (hept, J = 6.7 Hz, 1H), 0.78 (d, J = 6.7 Hz, 6H).	519.40

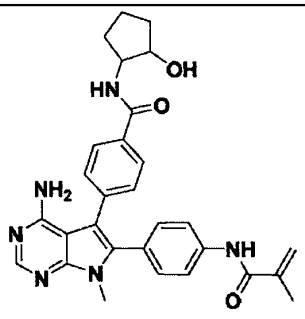
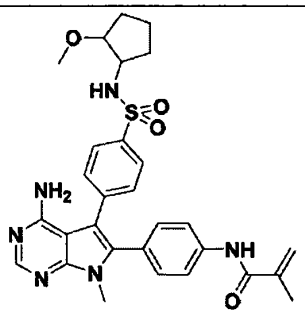
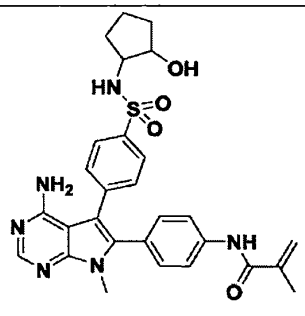
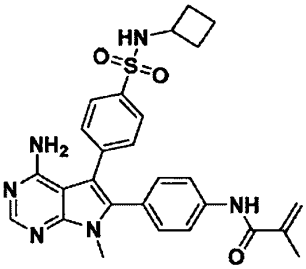
[0957]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(N-(氧杂环丁-3-基)胺磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.49 (d, J = 7.4 Hz, 1H), 8.22 (s, 1H), 7.75 - 7.67 (m, 4H), 7.42 - 7.35 (m, 2H), 7.27 - 7.19 (m, 2H), 5.97 (m, 2H), 5.82 - 5.77 (m, 1H), 5.53 (t, J = 1.5 Hz, 1H), 4.46 (dd, J = 7.6, 5.6 Hz, 2H), 4.40 (q, J = 7.1 Hz, 1H), 4.21 (t, J = 6.0 Hz, 2H), 3.62 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	519.35
N-(4-(4-氨基-5-(4-(N-环戊基胺磺酰亚胺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.85 - 7.79 (m, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.37 - 7.31 (m, 2H), 7.23 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.0 Hz, 1H), 5.90 (br, 2H), 5.77 (s, 1H), 5.55 (s, 1H), 4.04 (s, 1H), 3.63 (s, 3H), 3.40 - 3.60(m, 1H), 1.94 (t, J = 1.2 Hz, 3H), 1.49 (s, 4H), 1.33 (s, 2H), 1.15 (s, 2H).	530.20
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-磺酰亚胺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.82 - 7.76 (m, 2H), 7.73 - 7.66 (m, 2H), 7.41 - 7.34 (m, 2H), 7.26 - 7.18 (m, 2H), 5.79 (s, 3H), 5.56 - 5.50 (m, 1H), 4.37 (s, 1H), 3.63 (s, 3H), 3.06 (d, J = 6.4 Hz, 4H), 1.95 (d, J = 1.3 Hz, 3H), 1.61 - 1.53 (m, 4H).	516.30
N-(4-(4-氨基-5-(4-(N-环戊基-N-甲基胺磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.75 - 7.65 (m, 4H), 7.43 - 7.36 (m, 2H), 7.25 - 7.17 (m, 2H), 5.98 (s, 2H), 5.78 (t, J = 1.1 Hz, 1H), 5.56 - 5.51 (m, 1H), 4.17 (q, J = 8.0 Hz, 1H), 3.64 (s, 3H), 2.64 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H), 1.52 (q, J = 5.0, 4.5 Hz, 2H), 1.42 (d, J = 11.8 Hz, 4H), 1.32 - 1.23 (m, 2H).	545.40

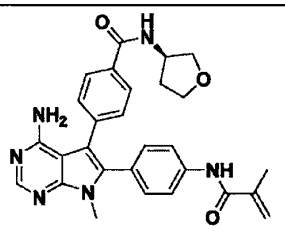
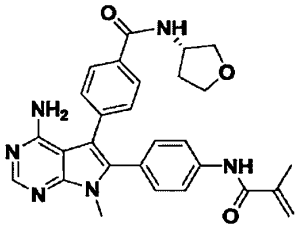
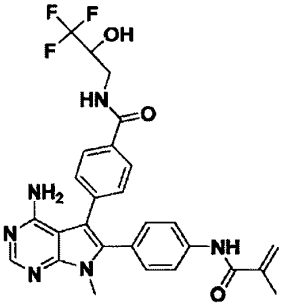
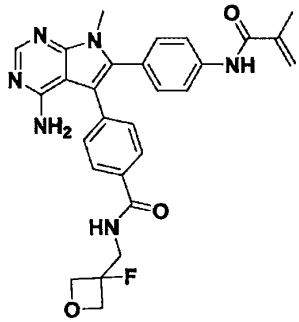
[0958]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(N-甲基-N-(2,2,2-三氟乙基)胺磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.23 (s, 1H), 7.83 - 7.76 (m, 2H), 7.76 - 7.69 (m, 2H), 7.45 - 7.38 (m, 2H), 7.29 - 7.21 (m, 2H), 5.83 - 5.78 (m, 1H), 5.54 (t, J = 1.4 Hz, 1H), 4.02 (q, J = 9.2 Hz, 2H), 3.62 (s, 3H), 2.83 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	559.40
N-(4-(4-氨基-5-(4-(环戊基甲磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.23 (s, 1H), 7.86 - 7.79 (m, 2H), 7.74 - 7.68 (m, 2H), 7.47 - 7.40 (m, 2H), 7.27 - 7.21 (m, 2H), 5.79 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 3.62 (s, 3H), 3.37 - 3.27 (m, 2H), 2.10 (hept, J = 7.5 Hz, 1H), 1.95 (d, J = 1.1 Hz, 3H), 1.75 - 1.63 (m, 2H), 1.54 (qd, J = 9.4, 8.0, 3.0 Hz, 2H), 1.45 (qt, J = 7.1, 2.6 Hz, 2H), 1.16 (dq, J = 11.8, 7.7 Hz, 2H).	530.4
N-(4-(4-氨基-7-甲基-5-(4-(3,3,3-三氟丙基磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.23 (s, 1H), 7.90 - 7.84 (m, 2H), 7.76 - 7.69 (m, 2H), 7.47 - 7.41 (m, 2H), 7.29 - 7.22 (m, 2H), 5.80 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 3.61 (s, 4H), 3.65 - 3.57 (m, 1H), 2.73 - 2.58 (m, 2H), 1.95 (s, 3H).	544.3
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基环戊基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.33 (d, J = 7.7 Hz, 1H), 8.21 (s, 1H), 7.79 (d, J = 7.9 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.28 (dd, J = 12.1, 8.1 Hz, 4H), 5.92 (s, 1H), 5.79 (s, 1H), 5.53 (s, 1H), 4.18 (dd, J = 11.6, 6.3 Hz, 1H), 3.69 (dd, J = 6.7, 3.4 Hz, 1H), 3.33 (s, 3H), 3.25 (s, 3H), 1.98 (d, J = 7.7 Hz, 1H), 1.95 (s, 3H), 1.88 (dq, J = 13.8, 7.0 Hz, 1H), 1.69 (s, 1H), 1.70 - 1.59 (m, 0H), 1.58 (s, 2H), 1.52 (dq, J = 14.1, 7.4, 6.3 Hz, 1H).	525.40

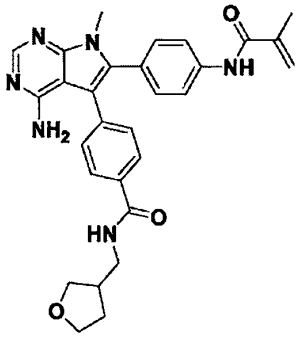
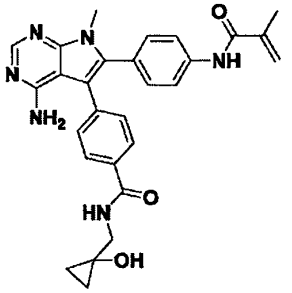
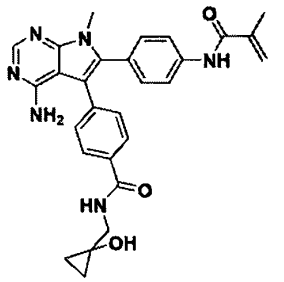
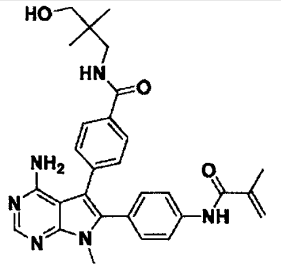
[0959]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-羟基环戊基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (d, J = 7.7 Hz, 2H), 7.83 - 7.76 (m, 2H), 7.73 - 7.67 (m, 2H), 7.32 - 7.22 (m, 4H), 5.90 (s, 1H), 5.79 (s, 1H), 5.53 (d, J = 2.0 Hz, 1H), 4.74 (d, J = 3.8 Hz, 1H), 3.98 (s, 2H), 3.61 (s, 3H), 2.03 - 1.92 (m, 4H), 1.91 - 1.78 (m, 1H), 1.65 (p, J = 7.8, 6.8 Hz, 2H), 1.47 (dd, J = 13.4, 7.0 Hz, 2H).	511.25
N-(4-(4-氨基-5-(4-(N-(2-甲氧基环戊基)胺磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.22 (s, 1H), 7.78 - 7.66 (m, 4H), 7.43 - 7.36 (m, 2H), 7.27 - 7.19 (m, 2H), 5.96 (s, 2H), 5.80 - 5.75 (m, 1H), 5.56 - 5.51 (m, 1H), 3.62 (s, 3H), 3.41 - 3.28 (m, 2H), 2.97 (s, 3H), 2.08 (s, 1H), 1.94 (d, J = 1.3 Hz, 3H), 1.76 - 1.57 (m, 1H), 1.61 - 1.44 (m, 1H), 1.48 - 1.36 (m, 3H), 1.21 (dt, J = 12.2, 6.4 Hz, 1H).	561.45
N-(4-(4-氨基-5-(4-(N-(2-羟基环戊基)胺磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.78 - 7.67 (m, 4H), 7.50 (d, J = 7.5 Hz, 1H), 7.42 - 7.35 (m, 2H), 7.27 - 7.20 (m, 2H), 5.94 (s, 1H), 5.78 (s, 1H), 5.53 (s, 1H), 4.66 (d, J = 4.4 Hz, 1H), 3.75 (dt, J = 8.7, 4.5 Hz, 1H), 3.58 (s, 1H), 3.32 (s, 2H), 3.24 - 3.17 (m, 1H), 1.95 (t, J = 1.2 Hz, 3H), 1.77 - 1.64 (m, 1H), 1.63 - 1.49 (m, 1H), 1.49 (d, J = 7.3 Hz, 2H), 1.35 (dt, J = 11.7, 5.7 Hz, 1H), 1.11 (dt, J = 13.1, 6.6 Hz, 1H).	547.35
N-(4-(4-氨基-5-(4-(N-环丁基胺磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.87 (d, J = 9.1 Hz, 1H), 7.75 - 7.65 (m, 4H), 7.38 (d, J = 8.3 Hz, 2H), 7.25 - 7.18 (m, 2H), 5.78 (s, 1H), 5.53 (s, 1H), 3.63 (s, 3H), 3.59 (d, J = 8.3 Hz, 0H), 3.32 (s, 1H), 1.94 (d, J = 1.5 Hz, 3H), 1.89 - 1.77 (m, 2H), 1.74 - 1.60 (m, 2H), 1.57 - 1.40 (m, 2H).	517.35

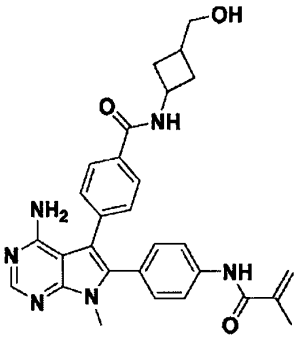
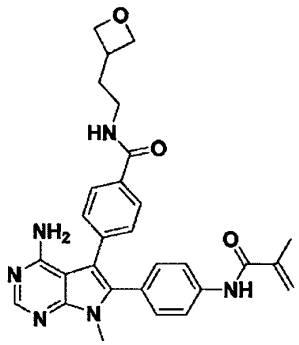
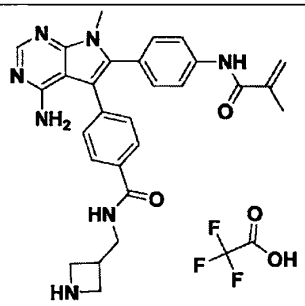
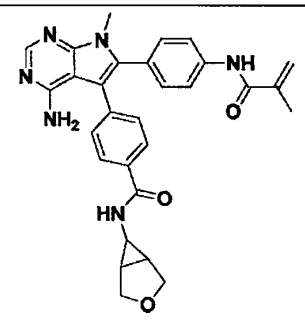
[0960]

化合物	结构	质子 NMR	MS [M+1]
(R)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.51 (d, J = 6.5 Hz, 1H), 8.21 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.32 - 7.23 (m, 4H), 5.79 (s, 1H), 5.53 (s, 1H), 4.44 (d, J = 7.2 Hz, 1H), 3.89 - 3.79 (m, 2H), 3.73 (m, 1H), 3.68 - 3.61 (m, 3H), 3.56 (dd, J = 8.8, 4.4 Hz, 1H), 2.18 - 2.07 (m, 1H), 1.97 - 1.87 (m, 4H).	497.20
(S)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.23 (s, 1H), 7.83 - 7.78 (m, 2H), 7.70 - 7.64 (m, 2H), 7.40 - 7.35 (m, 2H), 7.30 - 7.25 (m, 2H), 5.87 - 5.77 (m, 1H), 5.54 (dt, J = 2.0, 1.0 Hz, 1H), 4.59 (ddt, J = 8.0, 6.0, 4.1 Hz, 1H), 4.02 - 3.94 (m, 2H), 3.86 (td, J = 8.3, 5.8 Hz, 1H), 3.77 - 3.69 (m, 4H), 2.38 - 2.23 (m, 1H), 2.04 - 1.93 (d, J = 1.3 Hz, 4H).	497.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3,3,3-三氟-2-羟基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.70 (t, J = 5.7 Hz, 1H), 8.21 (s, 1H), 7.85 - 7.79 (m, 2H), 7.74 - 7.66 (m, 2H), 7.34 - 7.23 (m, 4H), 6.47 (d, J = 6.4 Hz, 1H), 5.92 (s, 1H), 5.79 (s, 1H), 5.53 (t, J = 1.4 Hz, 1H), 4.22 - 4.16 (m, 2H), 3.62 (s, 3H), 3.58 (d, J = 5.2 Hz, 1H), 1.95 (d, J = 1.2 Hz, 3H).	539.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((3-氟氧杂环丁-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.78 (t, J = 6.0 Hz, 1H), 8.21 (s, 1H), 7.86 - 7.79 (m, 2H), 7.74 - 7.66 (m, 2H), 7.34 - 7.29 (m, 2H), 7.29 - 7.22 (m, 2H), 5.79 (s, 1H), 5.53 (d, J = 2.1 Hz, 1H), 4.70 (d, J = 8.0 Hz, 1H), 4.65 (q, J = 3.4 Hz, 2H), 4.59 (d, J = 8.0 Hz, 1H), 3.82 (d, J = 6.0 Hz, 1H), 3.77 (d, J = 6.0 Hz, 1H), 3.61 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	515.40

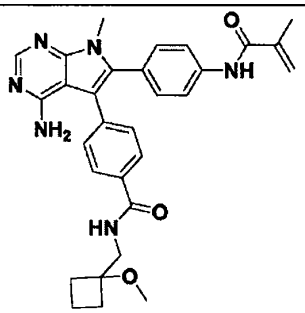
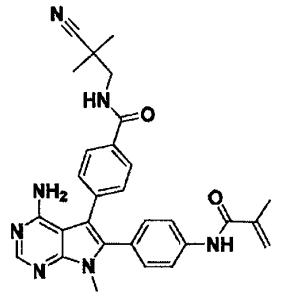
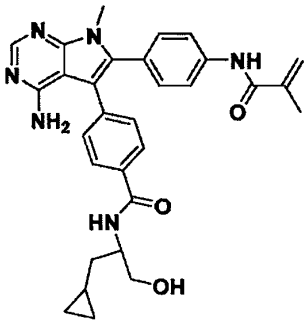
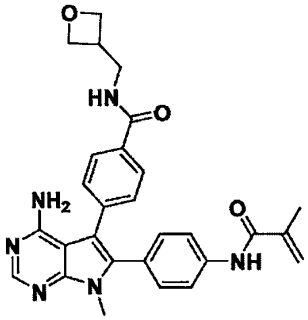
[0961]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((四氢呋喃-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.40 (s, 1H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.63 - 7.55 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.25 - 7.19 (m, 2H), 6.39 (t, *J* = 5.5 Hz, 1H), 5.82 (s, 1H), 5.52 (d, *J* = 2.0 Hz, 1H), 5.03 (s, 2H), 3.95 (td, *J* = 8.3, 5.2 Hz, 1H), 3.86 (dd, *J* = 8.9, 6.9 Hz, 1H), 3.82 - 3.72 (m, 4H), 3.66 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.50 (dd, *J* = 7.2, 5.3 Hz, 2H), 2.63 (p, *J* = 6.9 Hz, 1H), 2.19 - 2.05 (m, 4H), 1.78 - 1.66 (m, 1H).	511.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-羟基环丙基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.38 (t, *J* = 5.8 Hz, 1H), 8.21 (s, 1H), 7.86 - 7.79 (m, 2H), 7.74 - 7.66 (m, 2H), 7.33 - 7.23 (m, 4H), 5.80 (d, *J* = 1.4 Hz, 3H), 5.53 (t, *J* = 1.6 Hz, 1H), 5.40 (s, 1H), 3.67(s, 3H),3.42 (d, *J* = 5.7 Hz, 2H), 1.95 (t, *J* = 1.3 Hz, 3H), 0.55 (q, *J* = 2.2 Hz, 4H).	497.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-羟基环丙基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.38 (t, *J* = 5.8 Hz, 1H), 8.21 (s, 1H), 7.86 - 7.79 (m, 2H), 7.74 - 7.66 (m, 2H), 7.33 - 7.23 (m, 4H), 5.80 (d, *J* = 1.4 Hz, 3H), 5.53 (t, *J* = 1.6 Hz, 1H), 5.40 (s, 1H), 3.67(s, 3H),3.42 (d, *J* = 5.7 Hz, 2H), 1.95 (t, *J* = 1.3 Hz, 3H), 0.55 (q, *J* = 2.2 Hz, 4H).	497.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-羟基-2,2-二甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.38 (t, *J* = 6.2 Hz, 1H), 8.21 (s, 1H), 7.82 - 7.75 (m, 2H), 7.74 - 7.67 (m, 2H), 7.34 - 7.24 (m, 4H), 6.07 - 5.75 (m, 2H), 5.53 (t, *J* = 1.4 Hz, 1H), 4.58 (t, *J* = 6.1 Hz, 1H), 3.61 (s, 3H), 3.17 - 3.09 (m, 4H), 1.95 (t, *J* = 1.2 Hz, 3H), 0.83 (s, 6H).	513.30

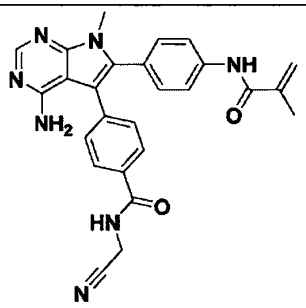
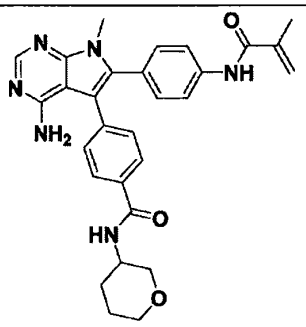
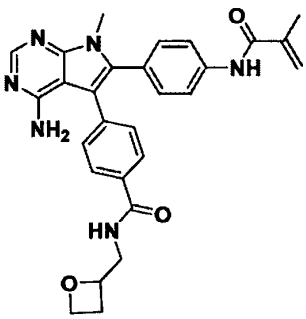
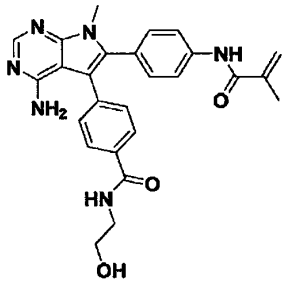
[0962]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-(羟基甲基)环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.53 (d, J = 7.5 Hz, 1H), 8.21 (s, 1H), 7.79 (dd, J = 8.4, 1.7 Hz, 2H), 7.73 - 7.67 (m, 2H), 7.32 - 7.22 (m, 4H), 5.79 (d, J = 1.3 Hz, 2H), 5.54 (d, J = 1.8 Hz, 1H), 4.51 - 4.38 (m, 1H), 4.27 (q, J = 8.4 Hz, 1H), 3.61 (s, 3H), 3.50 - 3.42 (m, 1H), 3.36 (t, J = 5.7 Hz, 2H), 2.25 (d, J = 8.8 Hz, 2H), 2.13 - 2.04 (m, 2H), 1.95 (d, J = 1.3 Hz, 3H), 1.82 - 1.70 (m, 1H).	511.30
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-(氧杂环丁-3-基)乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 7.3 Hz, 2H), 7.27 (d, J = 7.6 Hz, 4H), 5.80 (s, 2H), 5.53 (s, 1H), 4.67 (dd, J = 20.8, 5.0 Hz, 1H), 3.61 (s, 3H), 3.58 - 3.36 (m, 4H), 3.32 - 3.22 (m, 2H), 2.40 - 2.20 (m, 1H), 1.95 (t, J = 1.2 Hz, 3H), 1.88 (s, 1H), 1.64 (s, 1H).	511.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(氮杂环丁-3-基甲基)苯甲酰胺 2,2,2-三氟乙酸盐		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.68 (t, J = 5.8 Hz, 1H), 8.64 - 8.41 (m, 3H), 7.87 - 7.80 (m, 2H), 7.77 - 7.69 (m, 2H), 7.37 - 7.25 (m, 4H), 5.80 (s, 1H), 5.55 (d, J = 1.9 Hz, 1H), 3.95 (t, J = 10.1 Hz, 2H), 3.80 (q, J = 8.9, 7.9 Hz, 2H), 3.67 (s, 3H), 3.48 (t, J = 6.1 Hz, 2H), 3.01 (p, J = 7.5 Hz, 1H), 1.95 (t, J = 1.3 Hz, 3H).	496.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-氧杂双环[3.1.0]己-6-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.46 (d, J = 4.2 Hz, 1H), 8.21 (s, 1H), 7.79 - 7.73 (m, 2H), 7.73 - 7.66 (m, 2H), 7.32 - 7.22 (m, 4H), 5.90 (s, 1H), 5.79 (s, 1H), 5.56 - 5.51 (m, 1H), 3.86 (d, J = 8.4 Hz, 2H), 3.63 (d, J = 13.4 Hz, 5H), 2.59 (q, J = 2.9 Hz, 1H), 1.95 (t, J = 1.2 Hz, 3H),, 1.87 (s, 2H).	509.40

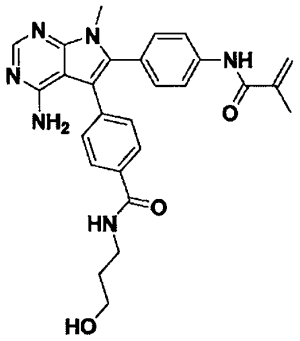
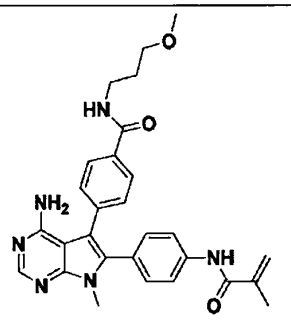
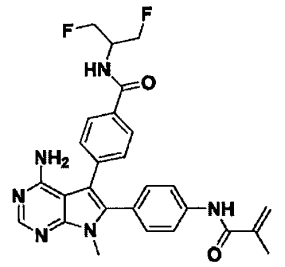
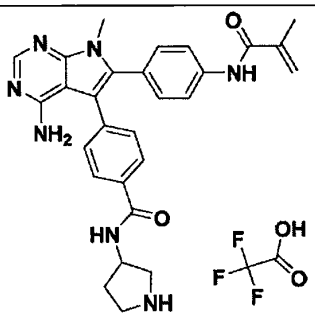
[0963]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-甲氧基环丁基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.27 (t, J = 6.1 Hz, 1H), 8.21 (s, 1H), 7.81 (d, J = 7.9 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.28 (dd, J = 11.9, 8.1 Hz, 4H), 5.80 (s, 2H), 5.53 (s, 1H), 3.53 (d, J = 6.0 Hz, 2H), 3.33 (s, 3H), 3.13 (s, 3H), 1.96 (d, J = 9.9 Hz, 7H), 1.70 - 1.64 (m, 1H), 1.63 - 1.54 (m, 1H).	525.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-氰基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.78 (t, J = 6.4 Hz, 1H), 8.22 (s, 1H), 7.86 - 7.80 (m, 2H), 7.75 - 7.67 (m, 2H), 7.36 - 7.24 (m, 4H), 5.80 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 3.61 (s, 3H), 3.46 (d, J = 6.4 Hz, 2H), 1.95 (d, J = 1.3 Hz, 3H), 1.33 (s, 6H).	508.2
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1-环丙基-3-羟基丙-2-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.85 - 7.78 (m, 2H), 7.74 - 7.67 (m, 2H), 7.32 - 7.23 (m, 4H), 5.95 (s, 2H), 5.79 (s, 1H), 5.56 - 5.51 (m, 1H), 4.63 (t, J = 5.8 Hz, 1H), 4.05 - 3.98 (m, 1H), 3.61 (s, 3H), 3.53 - 3.36 (m, 3H), 1.94 (d, J = 1.3 Hz, 3H), 1.44 (h, J = 7.4 Hz, 2H), 0.72 (s, 1H), 0.42 - 0.33 (m, 2H), 0.11 (d, J = 8.8 Hz, 1H).	525.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(氧杂环丁-3-基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.60 (t, J = 5.7 Hz, 1H), 8.21 (s, 1H), 7.82 - 7.75 (m, 2H), 7.74 - 7.67 (m, 2H), 7.33 - 7.23 (m, 4H), 5.92 (s, 1H), 5.80 (t, J = 1.0 Hz, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.63 (dd, J = 7.8, 6.0 Hz, 2H), 4.34 (t, J = 6.0 Hz, 2H), 3.61 (s, 3H), 3.53 (dd, J = 6.9, 5.7 Hz, 2H), 3.16 (dq, J = 13.7, 6.9 Hz, 1H), 1.95 (t, J = 1.2 Hz, 3H).	497.40

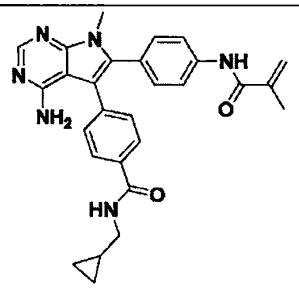
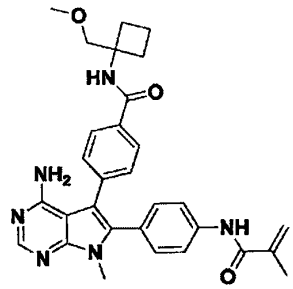
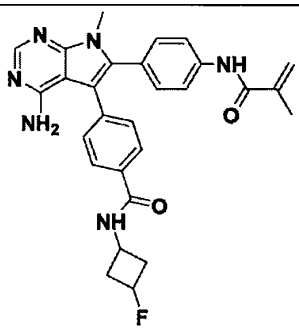
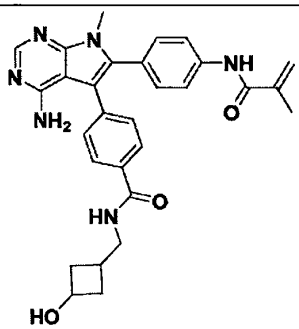
[0964]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(氰基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.18 (t, J = 5.5 Hz, 1H), 8.21 (s, 1H), 7.85 - 7.79 (m, 2H), 7.74 - 7.67 (m, 2H), 7.36 - 7.29 (m, 2H), 7.29 - 7.22 (m, 2H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 4.30 (d, J = 5.4 Hz, 2H), 3.61 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	466.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(四氢-2H-哌喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (d, J = 6.9 Hz, 2H), 7.83 - 7.76 (m, 2H), 7.74 - 7.66 (m, 2H), 7.32 - 7.22 (m, 4H), 5.91 (s, 2H), 5.79 (s, 1H), 5.56 - 5.51 (m, 1H), 3.93 - 3.86 (m, 1H), 3.83 - 3.72 (m, 2H), 3.61 (s, 3H), 3.28 - 3.22 (m, 1H), 3.14 (dd, J = 10.7, 9.5 Hz, 1H), 1.95 (t, J = 1.2 Hz, 4H), 1.69 (s, 1H), 1.58 (t, J = 9.3 Hz, 2H).	511.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(氧杂环丁-2-基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.61 (t, J = 5.8 Hz, 1H), 8.21 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.73 - 7.66 (m, 2H), 7.33 - 7.23 (m, 4H), 5.91 (s, 1H), 5.79 (s, 1H), 5.53 (s, 1H), 4.85 - 4.77 (m, 1H), 4.55 - 4.38 (m, 2H), 3.61 (s, 3H), 3.60 - 3.51 (m, 1H), 3.51 - 3.41 (m, 1H), 2.68 - 2.55 (m, 1H), 2.47 - 2.37 (m, 1H), 1.95 (d, J = 1.2 Hz, 3H).	497.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-羟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.73 - 7.66 (m, 2H), 7.27 (dd, J = 11.7, 8.3 Hz, 4H), 5.79 (s, 1H), 5.53 (s, 1H), 4.69 (t, J = 5.7 Hz, 1H), 3.61 (s, 3H), 3.50 (q, J = 6.2 Hz, 2H), 1.95 (s, 3H).	471.35

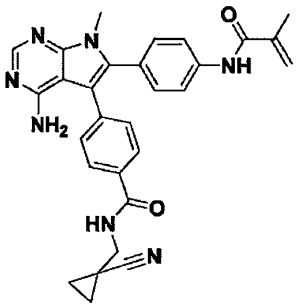
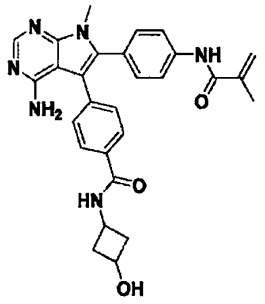
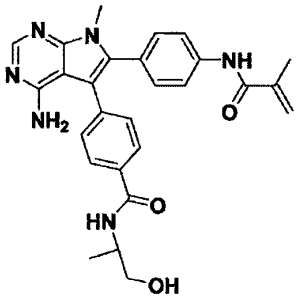
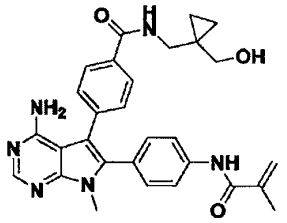
[0965]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-羟基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.42 (t, J = 5.6 Hz, 1H), 8.21 (s, 1H), 7.82 - 7.75 (m, 2H), 7.74 - 7.67 (m, 2H), 7.32 - 7.23 (m, 4H), 5.91 (s, 0H), 5.80 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.61 (s, 3H), 3.46 (q, J = 6.0 Hz, 2H), 3.34 (d, J = 6.0 Hz, 2H), 1.95 (t, J = 1.2 Hz, 3H), 1.67 (p, J = 6.6 Hz, 2H).	485.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-甲氧基丙基)苯甲酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.40 (s, 1H), 7.75 - 7.68 (m, 2H), 7.65 (s, 1H), 7.62 - 7.55 (m, 2H), 7.37 - 7.29 (m, 2H), 7.26 - 7.18 (m, 2H), 6.96 - 6.88 (m, 1H), 5.82 (s, 1H), 5.51 (q, J = 1.6 Hz, 1H), 5.03 (s, 2H), 3.74 (s, 3H), 3.59 (q, J = 5.8 Hz, 4H), 3.41 (s, 3H), 2.09 (t, J = 1.2 Hz, 3H), 1.96 - 1.86 (m, 2H).	499.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1,3-二氟丙-2-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.65 (d, J = 7.2 Hz, 1H), 8.21 (s, 1H), 7.87 - 7.81 (m, 2H), 7.74 - 7.67 (m, 2H), 7.35 - 7.29 (m, 2H), 7.29 - 7.23 (m, 2H), 5.94 (s, 1H), 5.80 (s, 1H), 5.53 (d, J = 1.9 Hz, 1H), 4.64 (t, J = 5.1 Hz, 2H), 4.53 (s, 3H), 3.62 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	505.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(吡咯烷-3-基)苯甲酰胺 2,2,2-三氟乙酸盐		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.84 (s, 2H), 8.60 (d, J = 6.2 Hz, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.87 - 7.80 (m, 2H), 7.76 - 7.70 (m, 2H), 7.37 - 7.31 (m, 2H), 7.31 - 7.24 (m, 2H), 5.80 (s, 1H), 5.55 (t, J = 1.5 Hz, 1H), 4.50 (hept, J = 6.0, 5.4 Hz, 1H), 3.67 (s, 3H), 3.41 (ddt, J = 28.8, 12.4, 6.4 Hz, 2H), 3.31 - 3.22 (m, 1H), 3.21 - 3.12 (m, 1H), 2.26 - 2.13 (m, 1H), 2.01 (dt, J = 13.1, 6.4 Hz, 1H), 1.95 (t, J = 1.2 Hz, 3H).	496.40

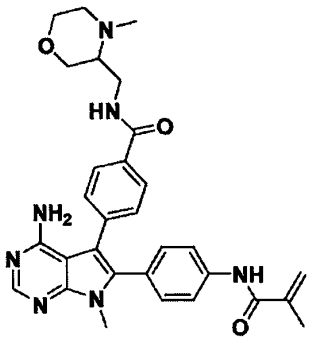
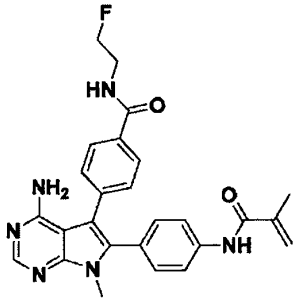
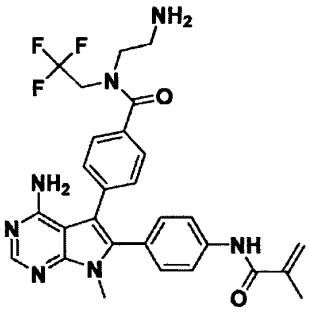
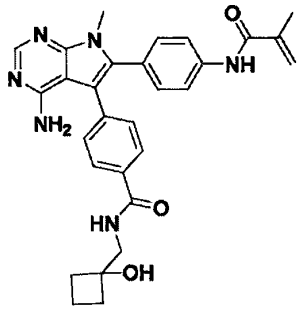
[0966]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丙基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.67 (dd, J = 7.2, 3.8 Hz, 1H), 8.21 (s, 1H), 7.79 (dd, J = 8.3, 2.7 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.33 - 7.22 (m, 4H), 5.92 (s, 2H), 5.79 (s, 1H), 5.53 (d, J = 2.0 Hz, 1H), 3.97 (q, J = 7.9 Hz, 1H), 3.61 (s, 3H), 2.72 (ddd, J = 9.6, 6.5, 3.1 Hz, 1H), 2.46 (s, 1H), 2.33 - 2.20 (m, 1H), 1.94 (d, J = 1.4 Hz, 3H).	481.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1-(甲氧基甲基)环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 7.84 - 7.78 (m, 2H), 7.74 - 7.66 (m, 2H), 7.30 - 7.22 (m, 4H), 5.80 (d, J = 1.3 Hz, 1H), 5.56 - 5.51 (m, 1H), 3.61 (d, J = 1.4 Hz, 5H), 3.31 (d, J = 13.6 Hz, 3H), 2.30 - 2.18 (m, 2H), 2.18 - 2.09 (m, 2H), 1.95 (d, J = 1.3 Hz, 3H), 1.85 (dd, J = 9.4, 4.8 Hz, 1H), 1.84 - 1.72 (m, 1H).	525.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-氟环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.67 (dd, J = 7.2, 3.8 Hz, 1H), 8.21 (s, 1H), 7.79 (dd, J = 8.3, 2.7 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.33 - 7.22 (m, 4H), 5.92 (s, 2H), 5.79 (s, 1H), 5.53 (d, J = 2.0 Hz, 1H), 3.97 (q, J = 7.9 Hz, 1H), 3.61 (s, 3H), 2.72 (ddd, J = 9.6, 6.5, 3.1 Hz, 1H), 2.46 (s, 1H), 2.33 - 2.20 (m, 1H), 1.94 (d, J = 1.4 Hz, 3H).	499.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((3-羟基环丁基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.43 (t, J = 5.9 Hz, 1H), 8.21 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.28 (dd, J = 10.3, 8.3 Hz, 4H), 5.79 (s, 3H), 5.53 (s, 1H), 4.92 (s, 1H), 3.91 - 3.83 (m, 1H), 3.61 (s, 3H), 3.25 (t, J = 6.2 Hz, 2H), 2.23 (p, J = 7.6, 7.1 Hz, 2H), 1.95 - 1.90 (s, 4H), 1.59 - 1.47 (m, 2H), 1.24 (s, 0H).	511.40

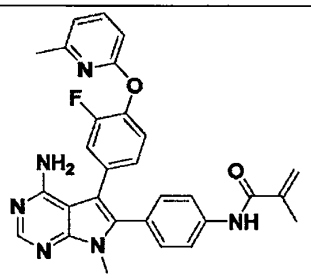
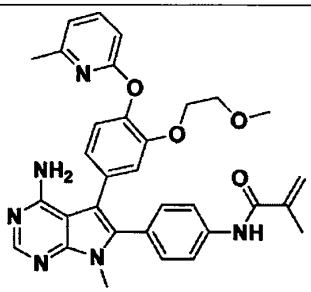
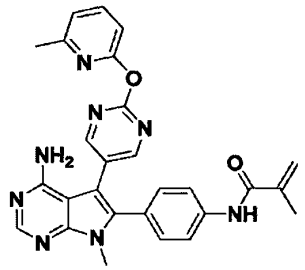
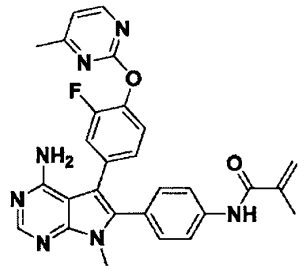
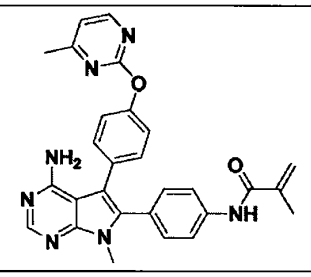
[0967]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-氰基环丙基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.87 (t, J = 6.1 Hz, 1H), 8.21 (s, 1H), 7.86 - 7.79 (m, 2H), 7.74 - 7.66 (m, 2H), 7.35 - 7.29 (m, 2H), 7.29 - 7.23 (m, 2H), 5.92 (s, 2H), 5.79 (s, 1H), 5.53 (d, J = 2.0 Hz, 1H), 3.61 (s, 3H), 3.42 (d, J = 5.9 Hz, 2H), 1.94 (t, J = 1.3 Hz, 3H), 1.21 (q, J = 3.9, 2.9 Hz, 2H), 1.18 - 1.08 (m, 2H).	506.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-羟基环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.55 (t, J = 8.4 Hz, 1H), 8.21 (s, 1H), 7.79 (dd, J = 8.4, 2.0 Hz, 2H), 7.74 - 7.67 (m, 2H), 7.27 (td, J = 8.7, 2.2 Hz, 4H), 5.79 (s, 1H), 5.56 - 5.51 (m, 1H), 5.07 (d, J = 5.5 Hz, 1H), 3.86 (d, J = 7.7 Hz, 1H), 3.61 (s, 3H), 2.30 - 2.21 (m, 1H), 2.01 - 1.83 (m, 4H).	497.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1-羟基丙-2-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.27 (t, J = 8.8 Hz, 4H), 5.89 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 4.69 (t, J = 5.8 Hz, 1H), 4.01 (q, J = 6.7 Hz, 1H), 3.61 (s, 3H), 3.45 (dt, J = 11.2, 5.8 Hz, 1H), 3.37 - 3.27 (m, 1H), 1.95 (t, J = 1.3 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H).	485.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-(羟基甲基)环丙基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.37 (s, 1H), 7.78 - 7.69 (m, 3H), 7.57 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 5.9 Hz, 1H), 5.83 (s, 1H), 5.51 (d, J = 1.8 Hz, 1H), 5.09 (s, 2H), 3.73 (s, 3H), 3.51 - 3.43 (m, 4H), 2.08 (s, 3H), 0.60 - 0.49 (m, 4H).	511.30

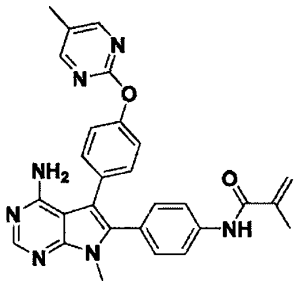
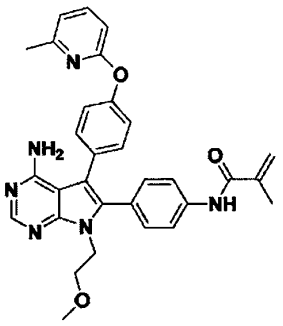
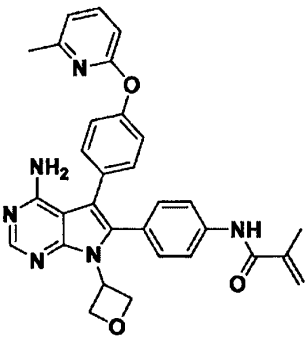
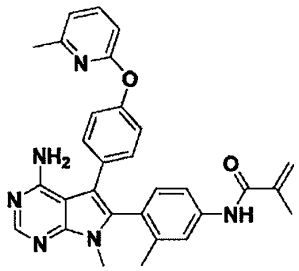
[0968]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((4-甲基吗啉-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.37 (t, J = 5.9 Hz, 1H), 8.21 (s, 1H), 7.81 - 7.74 (m, 2H), 7.73 - 7.66 (m, 2H), 7.33 - 7.23 (m, 4H), 5.79 (s, 1H), 5.53 (s, 1H), 3.74 - 3.62 (m, 2H), 3.61 (s, 3H), 3.57 - 3.41 (m, 2H), 3.23 (dd, J = 11.3, 9.3 Hz, 1H), 3.13 (dt, J = 13.3, 6.4 Hz, 1H), 2.63 (d, J = 11.7 Hz, 1H), 2.29 (s, 3H), 2.21 - 2.11 (m, 2H), 1.94 (t, J = 1.2 Hz, 3H).	540.30
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.68 (d, J = 6.1 Hz, 1H), 8.21 (s, 1H), 7.82 (d, J = 7.9 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.28 (dd, J = 16.5, 8.1 Hz, 4H), 5.80 (s, 2H), 5.53 (s, 1H), 4.59 (t, J = 5.2 Hz, 1H), 4.47 (t, J = 5.2 Hz, 1H), 3.62 (s, 3H), 3.59 (d, J = 5.4 Hz, 1H), 3.59 - 3.50 (m, 1H), 1.95 (s, 3H).	473.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-氨基乙基)-N-(2,2,2-三氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.46 (s, 1H), 7.86 (s, 3H), 7.73 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 7.29 (dd, J = 19.9, 8.0 Hz, 4H), 5.80 (s, 1H), 5.54 (d, J = 1.7 Hz, 1H), 4.25 (s, 2H), 3.68 (m, 5H), 3.08 (s, 2H), 1.94 (d, J = 1.5 Hz, 3H).	552.2
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-羟基环丁基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.31 (t, J = 5.9 Hz, 1H), 8.21 (s, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.74 - 7.67 (m, 2H), 7.33 - 7.23 (m, 4H), 5.92 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 5.15 (s, 1H), 3.61 (s, 3H), 3.41 (d, J = 6.0 Hz, 2H), 2.10 - 1.99 (m, 2H), 1.95 (d, J = 1.3 Hz, 3H), 1.89 (dd, J = 11.6, 8.9 Hz, 2H), 1.63 (d, J = 9.9 Hz, 1H), 1.48 (q, J = 9.2 Hz, 1H).	511.40

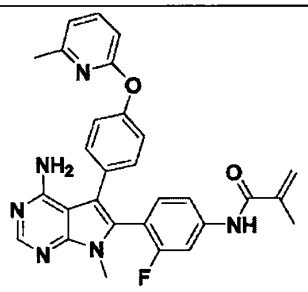
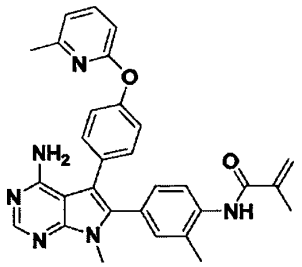
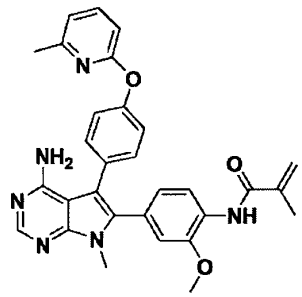
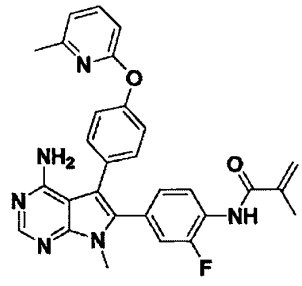
[0969]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d4) δ 8.22 (s, 1H), 7.75 - 7.71 (m, 3H), 7.35 - 7.33 (m, 1H), 7.22 (t, J = 8.4 Hz, 1H), 7.16 - 7.11 (m, 2H), 7.00 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 5.83 (s, 1H), 5.55 (s, 1H), 3.71 (s, 3H), 2.39 (s, 3H), 2.05 (s, 3H).	509.30
N-(4-(4-氨基-5-(3-(2-甲氧基乙氧基)-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.20 (s, 1H), 7.78 - 7.71 (m, 2H), 7.70 - 7.62 (m, 1H), 7.35 - 7.28 (m, 2H), 7.08 (d, J = 8.2 Hz, 1H), 6.97 - 6.90 (m, 2H), 6.84 (dd, J = 8.2, 2.0 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 5.79 (s, 1H), 5.53 (s, 1H), 3.88 (dd, J = 5.6, 3.8 Hz, 2H), 3.62 (s, 3H), 3.31 - 3.25 (m, 2H), 3.06 (s, 3H), 2.30 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	565.40
N-(4-(4-氨基-7-甲基-5-(2-((6-甲基吡啶-2-基)氧基)嘧啶-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.39 (s, 2H), 8.21 (s, 1H), 7.91 - 7.64 (m, 3H), 7.31 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 7.4 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.33 (s, 2H), 5.82 (s, 1H), 5.55 (d, J = 1.9 Hz, 1H), 3.60 (s, 3H), 2.42 (s, 3H), 1.96 (s, 3H).	493.20
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.78 - 7.66 (m, 2H), 7.33 (m, J = 8.6, 2.3 Hz, 3H), 7.21 - 7.16 (m, 2H), 7.12 (s, 0H), 5.80 (s, 1H), 5.54 (d, J = 1.7 Hz, 1H), 3.59 (s, 3H), 2.42 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	510.20
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.82 - 7.68 (m, 2H), 7.37 - 7.26 (m, 4H), 7.24 - 7.12 (m, 3H), 5.79 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 3.60 (s, 3H), 2.41 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	492.20

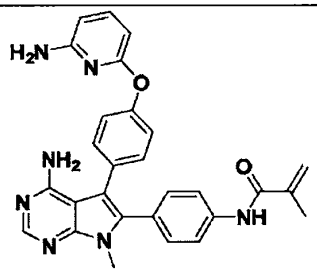
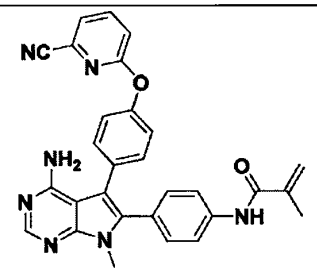
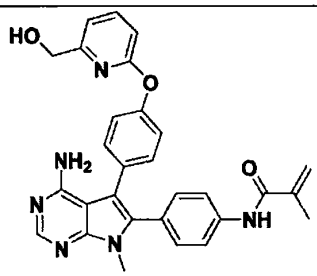
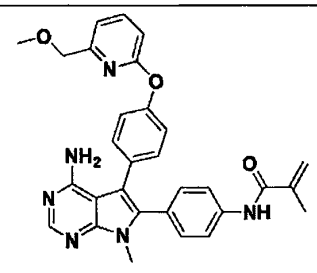
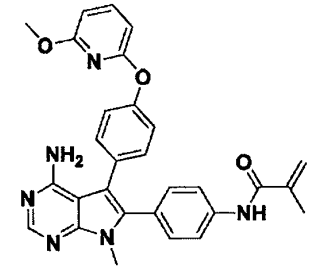
[0970]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(5-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.50 (d, J = 0.9 Hz, 2H), 8.20 (s, 1H), 7.81 - 7.67 (m, 2H), 7.39 - 7.25 (m, 4H), 7.25 - 7.12 (m, 2H), 6.2 - 5.67 (t, J = 1.0 Hz, 2H), 5.54 (t, J = 1.5 Hz, 1H), 3.60 (s, 3H), 2.22 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	492.20
N-(4-(4-氨基-7-(2-甲氧基乙基)-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.19 (s, 1H), 7.73 (dd, J = 8.4, 7.3 Hz, 3H), 7.34 - 7.27 (m, 2H), 7.31 - 7.21 (m, 2H), 7.10 - 7.03 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 5.82 - 5.77 (m, 1H), 5.69 (s, 1H), 5.53 (t, J = 1.4 Hz, 1H), 4.25 (t, J = 6.0 Hz, 2H), 3.50 (t, J = 6.0 Hz, 2H), 3.09 (s, 3H), 2.34 (s, 3H), 2.08 (s, 1H), 1.95 (t, J = 1.2 Hz, 3H).	535.25
N-(4-(4-氨基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7-(氧杂环丁-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.20 (s, 1H), 7.77 - 7.68 (m, 3H), 7.24 (dd, J = 8.6, 3.1 Hz, 4H), 7.10 - 7.05 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.79 (s, 1H), 5.63 - 5.51 (m, 2H), 5.15 (t, J = 6.9 Hz, 2H), 4.61 (dd, J = 7.9, 6.2 Hz, 2H), 2.34 (s, 3H), 1.95 (d, J = 1.6 Hz, 3H).	533.2
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.20 (s, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.65 - 7.56 (m, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.24 - 7.16 (m, 2H), 7.09 - 7.02 (m, 2H), 7.00 (d, J = 7.3 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.79 (s, 1H), 5.52 (t, J = 1.5 Hz, 1H), 3.32 (s, 3H), 2.33 (s, 3H), 1.97 - 1.91 (m, 6H).	505.25

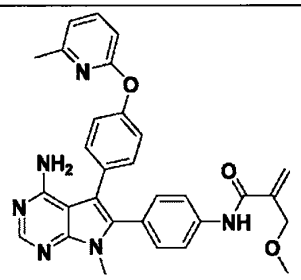
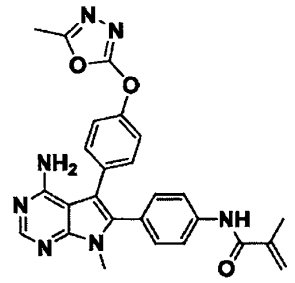
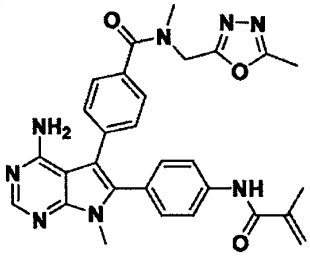
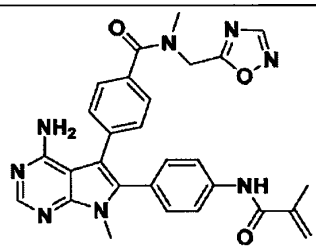
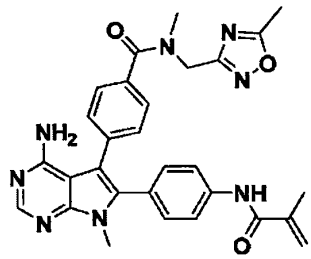
[0971]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.21 (s, 1H), 7.81 - 7.69 (m, 2H), 7.51 (dd, J = 8.5, 2.0 Hz, 1H), 7.34 - 7.21 (m, 3H), 7.09 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.82 (s, 1H), 5.58 (s, 1H), 3.55 (s, 3H), 2.34 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	509.50
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.19 (s, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.30 - 7.21 (m, 3H), 7.16 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.85 (s, 1H), 5.50 (s, 1H), 3.32 (s, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 1.96 (s, 3H).	505.20
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲氧基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.20 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.13 - 7.06 (m, 2H), 7.04 - 6.93 (m, 3H), 6.79 (d, J = 8.1 Hz, 1H), 5.95 (s, 1H), 5.84 (s, 1H), 5.51 (d, J = 1.7 Hz, 1H), 3.69 (d, J = 6.4 Hz, 6H), 2.33 (s, 3H), 1.96 (d, J = 1.5 Hz, 3H).	521.10
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.21 (s, 1H), 7.81 - 7.69 (m, 2H), 7.51 (dd, J = 8.6, 2.1 Hz, 1H), 7.27 (dd, J = 23.5, 8.5 Hz, 3H), 7.09 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.82 (s, 1H), 5.58 (s, 1H), 3.55 (s, 3H), 2.34 (s, 3H), 1.95 (s, 3H).	509.50

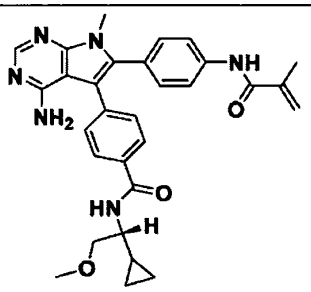
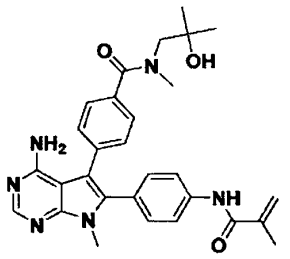
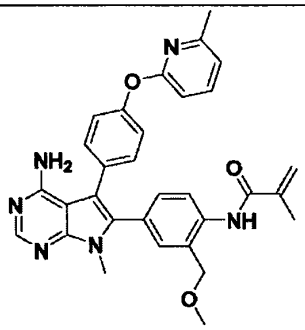
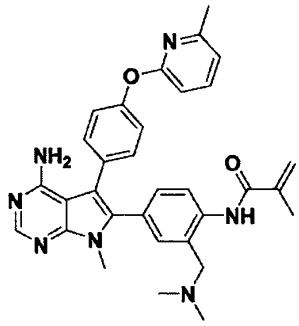
[0972]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((6-氨基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.19 (s, 1H), 7.75 - 7.68 (m, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.27 - 7.19 (m, 2H), 7.05 - 6.97 (m, 2H), 6.18 (d, J = 7.9 Hz, 1H), 6.05 - 5.97 (m, 3H), 5.80 (s, 1H), 5.67 (s, 2H), 5.53 (t, J = 1.5 Hz, 1H), 3.60 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	492.25
N-(4-(4-氨基-5-(4-((6-氰基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.21 (s, 1H), 8.09 (dd, J = 8.4, 7.2 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.77 - 7.67 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.35 - 7.26 (m, 4H), 7.26 - 7.08 (m, 2H), 5.80 (s, 2H), 5.58 - 5.45 (m, 1H), 3.61 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	502.20
N-(4-(4-氨基-5-(4-((6-(羟基甲基)吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.76 - 7.68 (m, 2H), 7.33 - 7.21 (m, 5H), 7.14 - 7.06 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 5.93 (s, 2H), 5.80 (s, 1H), 5.54 (t, J = 1.5 Hz, 1H), 5.38 (t, J = 5.8 Hz, 1H), 4.42 (d, J = 5.0 Hz, 2H), 3.62 (s, 3H), 1.96 (d, J = 1.3 Hz, 3H).	507.30
N-(4-(4-氨基-5-(4-((6-(甲氧基甲基)吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.86 (t, J = 7.8 Hz, 1H), 7.77 - 7.68 (m, 2H), 7.33 - 7.22 (m, 4H), 7.20 - 7.05 (m, 3H), 6.91 (d, J = 8.2 Hz, 1H), 5.80 (s, 1H), 5.56 - 5.51 (m, 1H), 4.35 (s, 2H), 3.62 (s, 3H), 3.33 (d, J = 6.5 Hz, 4H), 1.95 (t, J = 1.3 Hz, 3H).	521.25
N-(4-(4-氨基-5-(4-((6-甲氧基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.75 - 7.62 (m, 3H), 7.33 - 7.19 (m, 4H), 7.15 - 7.01 (m, 2H), 6.52 (d, J = 7.9 Hz, 2H), 6.26 - 5.68 (m, 1H), 5.57 - 5.43 (m, 1H), 3.62 (s, 5H), 1.95 (d, J = 1.3 Hz, 3H).	507.20

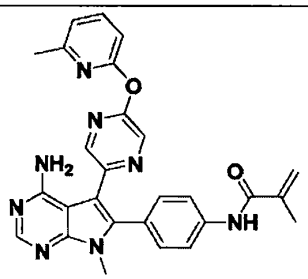
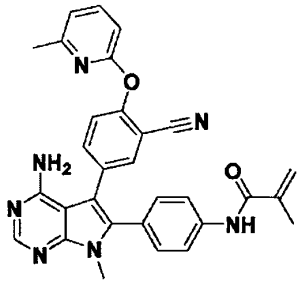
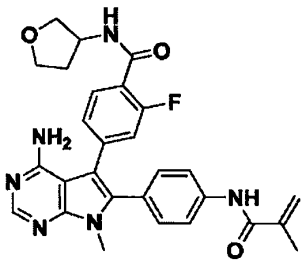
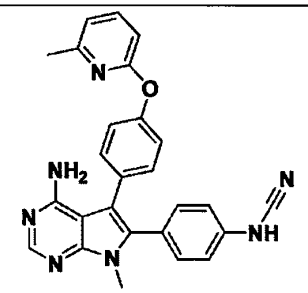
[0973]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-(甲氧基甲基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.19 (s, 1H), 7.84 - 7.58 (m, 3H), 7.35 - 7.20 (m, 4H), 7.13 - 7.05 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.94 (s, 1H), 5.70 (s, 1H), 4.15 (s, 2H), 3.61 (s, 3H), 3.31 (d, J = 7.2 Hz, 3H), 2.34 (s, 3H).	521.30
N-(4-(4-氨基-7-甲基-5-(4-((5-甲基-1,3,4-恶二唑-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d4) δ 8.21 (s, 1H), 7.69 - 7.67 (m, 2H), 7.40 (s, 4H), 7.31 - 7.29 (m, 2H), 5.82 (s, 1H), 5.54 (d, J = 1.6 Hz, 1H), 3.71 (s, 3H), 2.50 (s, 3H), 2.04 (s, 3H).	482.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((5-甲基-1,3,4-恶二唑-2-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.40 (s, 1H), 7.62 - 7.56 (m, 3H), 7.48 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 5.83 (s, 1H), 5.52 (s, 1H), 5.04 (s, 2H), 4.94 (s, 2H), 3.74 (s, 3H), 3.14 (s, 3H), 2.58 (s, 3H), 2.09 (t, J = 1.3 Hz, 3H)	537.35
N-((1,2,4-恶二唑-5-基)甲基)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.60 (s, 1H), 8.21 (s, 1H), 8.17 - 8.10 (m, 2H), 7.74 - 7.67 (m, 2H), 7.34 - 7.23 (m, 4H), 5.91 (s, 1H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 4.15 (s, 2H), 3.62 (s, 3H), 3.07 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	523.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((5-甲基-1,2,4-恶二唑-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.4 Hz, 4H), 5.80 (s, 1H), 5.53 (s, 1H), 4.76 (s, 1H), 4.62 (s, 1H), 3.61 (s, 3H), 3.03 (s, 2H), 2.96 (s, 1H), 2.60 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	537.2

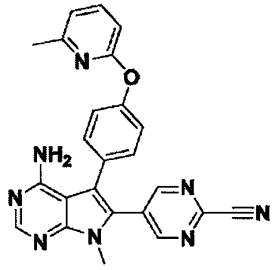
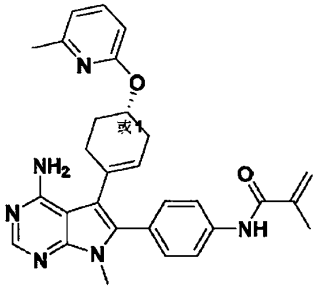
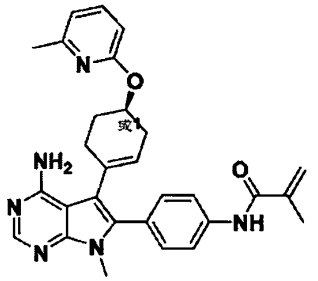
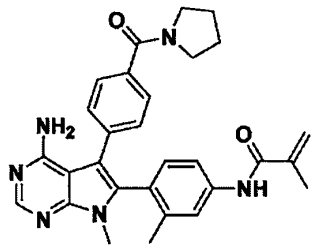
[0974]

化合物	结构	质子 NMR	MS [M+1]
(R)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1-环丙基-2-甲氧基乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.21 (s, 1H), 7.83 - 7.77 (m, 2H), 7.73 - 7.67 (m, 2H), 7.32 - 7.23 (m, 4H), 5.79 (s, 3H), 5.53 (d, J = 1.7 Hz, 1H), 3.68 - 3.61 (m, 4H), 3.48 (qd, J = 9.9, 6.2 Hz, 2H), 3..24(s, 3H), 1.95 (d, J = 1.2 Hz, 3H), 0.95 (dd, J = 8.1, 5.0 Hz, 1H), 0.45 (dt, J = 8.7, 4.1 Hz, 1H), 0.37 - 0.22 (m, 3H).	525.30
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-羟基-2-甲基丙基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.35 (s, 1H), 7.60 (d, J = 8.0 Hz, 3H), 7.44 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 5.83 (s, 1H), 5.52 (d, J = 1.5 Hz, 1H), 3.75 (s, 3H), 3.62 (s, 2H), 3.14 (s, 3H), 2.09 (t, J = 1.2 Hz, 3H), 1.33 (s, 6H), 1.01 (s, 1H).	513.45
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-(甲氧基甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.20 (s, 1H), 7.85 - 7.63 (m, 2H), 7.51 - 7.18 (m, 4H), 7.15 - 7.06 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.85 (s, 1H), 5.54 (t, J = 1.6 Hz, 1H), 4.45 (s, 2H), 3.63 (s, 3H), 3.20 (s, 3H), 2.33 (d, J = 5.9 Hz, 3H), 1.98 (s, 3H).	535.30
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-((二甲基氨基)甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 11.20 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.35 (dd, J = 8.5, 2.0 Hz, 1H), 7.27 - 7.20 (m, 2H), 7.10 - 7.04 (m, 3H), 7.01 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.85 (s, 1H), 5.71 (s, 2H), 5.54 (t, J = 1.6 Hz, 1H), 3.65 (s, 3H), 3.47 (s, 2H), 2.35 (s, 3H), 2.14 (s, 6H), 1.99 (s, 3H).	548.30

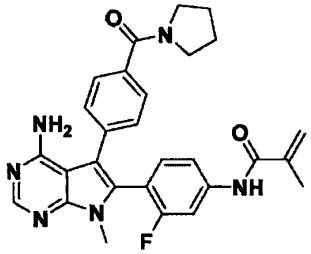
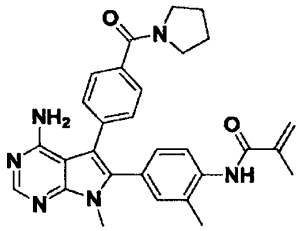
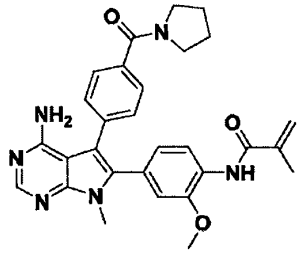
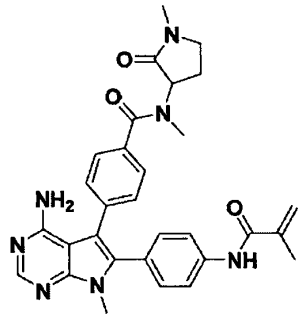
[0975]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(5-((6-甲基吡啶-2-基)氧基)吡嗪-2-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.63 (s, 1H), 8.20 (s, 1H), 7.83 (dd, J = 31.7, 8.0 Hz, 3H), 7.66 (s, 1H), 7.59 - 7.28 (m, 4H), 7.12 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 5.83 (s, 1H), 5.56 (s, 1H), 3.57 (s, 3H), 2.35 (s, 3H), 1.97 (s, 3H).	493.20
N-(4-(4-氨基-5-(3-氰基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.92 (s, 1H), 8.27 (s, 1H), 7.82 (t, J = 7.8 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.71 (s, 1H), 7.47 (dd, J = 8.7, 2.2 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.63 (s, 3H), 2.35 (s, 3H), 1.96 (s, 3H).2.44 (s, 3H), 1.96 (d, J = 1.2 Hz, 3H).	516.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, 甲醇-d4) δ 8.23 (s, 1H), 7.71 - 7.69 (m, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.31 - 7.27 (m, 2H), 7.21 (dd, J_1 = 8.0Hz, J_2 = 1.2 Hz, 1H), 7.09 (dd, J_1 = 11.6Hz, J_2 = 1.2 Hz, 1H), 5.82 (t, J = 1.0 Hz, 1H), 5.55 (d, J = 1.8 Hz, 1H), 4.58 - 4.55(m, 1H), 3.98 - 3.93 (m, 2H), 3.87 - 3.83 (m, 1H), 3.75 - 3.71 (m, 1H), 3.70 (s, 1H), 2.33 - 2.30(m, 1H), 2.05(s, 3H), 1.97 - 1.96(m, 1H).	515.35
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)氰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.19 (s, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.28 - 7.21 (m, 2H), 7.13 - 7.05 (m, 2H), 7.02 (d, J = 7.3 Hz, 1H), 6.98 - 6.91 (m, 2H), 6.78 (d, J = 8.1 Hz, 1H), 5.90 (s, 2H), 3.60 (s, 3H), 2.35 (s, 3H).	448.20

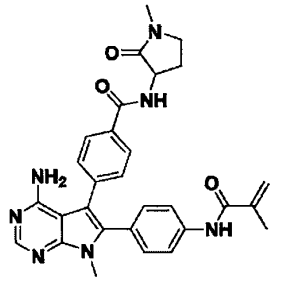
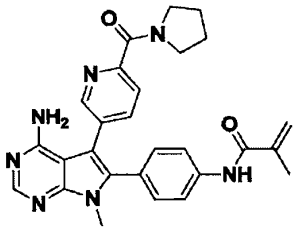
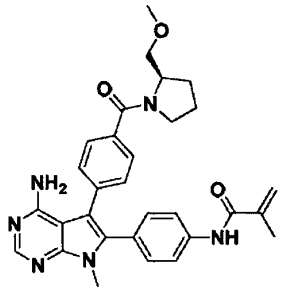
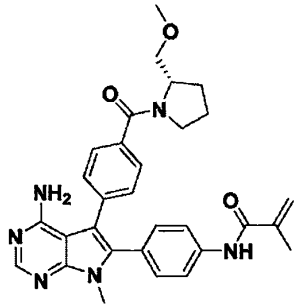
[0976]

化合物	结构	质子 NMR	MS [M+1]
5-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)嘧啶-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 2H), 8.26 (s, 1H), 7.75 (s, 1H), 7.47 - 7.26 (m, 2H), 7.25 - 7.10 (m, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 3.76 (s, 3H), 2.36 (s, 3H).	435.20
(S)-N-(4-(4-氨基-5-(1-(4-(二甲基氨基)-2-甲基丁酰基)哌啶-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d4) δ 8.15 (s, 1H), 7.81 - 7.79 (m, 2H), 7.56 - 7.48 (m, 3H), 6.77 (d, J = 7.2 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 5.87 - 5.85 (m, 2H), 5.57 - 5.56 (m, 1H), 5.39 - 5.37 (m, 1H), 3.67 (s, 3H), 2.67 - 2.62 (m, 1H), 2.47 - 2.45 (m, 1H), 2.41(s, 3H), 2.28 - 2.23 (m, 1H), 2.08 (s, 3H), 2.07 - 2.02 (m, 2H), 1.86 (d, J = 6.4 Hz, 1H).	495.40
(R)-N-(4-(4-氨基-5-(1-(4-(二甲基氨基)-2-甲基丁酰基)哌啶-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d4) δ 8.15 (s, 1H), 7.81 - 7.79 (m, 2H), 7.56 - 7.48 (m, 3H), 6.78 (d, J = 7.2 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 5.87 - 5.85 (m, 2H), 5.57 (d, J = 1.7 Hz, 1H), 5.39 - 5.37 (m, 1H), 3.67 (s, 3H), 2.67 - 2.62 (m, 1H), 2.47 - 2.45 (m, 1H), 2.41(s, 3H), 2.28 - 2.23 (m, 1H), 2.08 (s, 3H), 2.07 - 2.02 (m, 2H), 1.86 (m, 1H).	495.40
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.21 (s, 1H), 7.61 (s, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.23 (dd, J = 18.0, 8.2 Hz, 3H), 5.80 (s, 2H), 5.52 (s, 1H), 3.43 (s, 7H), 1.95 (s, 3H), 1.90 (s, 3H), 1.88 - 1.68 (m, 4H).	495.30

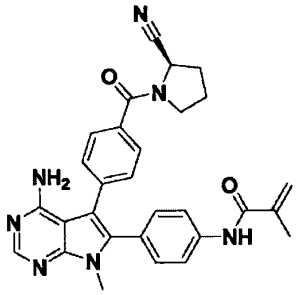
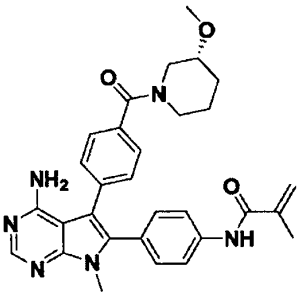
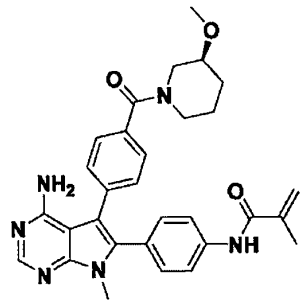
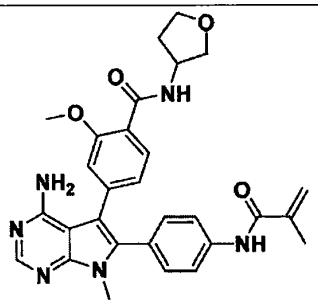
[0977]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.22 (s, 1H), 7.76 (dd, J = 12.4, 2.0 Hz, 1H), 7.48 (dd, J = 8.4, 1.6 Hz, 3H), 7.31 - 7.21 (m, 3H), 6.01 (s, 1H), 5.82 (s, 1H), 5.57 (s, 1H), 3.55 (s, 3H), 3.43 (dt, J = 17.2, 6.6 Hz, 4H), 1.95 (t, J = 1.2 Hz, 3H), 1.83 (dt, J = 17.8, 7.4 Hz, 4H).	499.35
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.21 (s, 1H), 7.63 - 7.40 (m, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.30 - 7.24 (m, 2H), 7.22 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 8.0, 2.0 Hz, 1H), 5.85 (s, 1H), 5.50 (s, 1H), 3.62 (s, 3H), 3.43 (d, J = 21.0 Hz, 4H), 2.15 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H), 1.88 - 1.68 (m, 4H).	495.30
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲氧基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.21 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.33 - 7.26 (m, 2H), 6.94 (d, J = 6.6 Hz, 2H), 5.85 (s, 1H), 5.54 - 5.48 (m, 1H), 3.67 (d, J = 2.8 Hz, 6H), 3.44 (dt, J = 18.4, 6.6 Hz, 4H), 1.96 (d, J = 1.4 Hz, 3H), 1.90 - 1.79 (m, 4H).	511.30
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-(1-甲基-2-侧氧基吡咯烷-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.74 - 7.66 (m, 2H), 7.38 (d, J = 7.7 Hz, 2H), 7.29 - 7.22 (m, 4H), 5.80 (s, 1H), 5.53 (s, 1H), 4.58 (t, J = 9.3 Hz, 1H), 3.61 (s, 3H), 3.32 (d, J = 8.7 Hz, 1H), 3.18 (d, J = 8.7 Hz, 1H), 2.77 (t, J = 13.3 Hz, 6H), 2.16 (s, 2H), 1.95 (s, 3H).	538.35

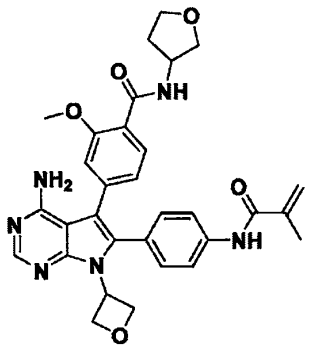
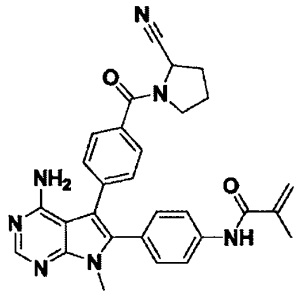
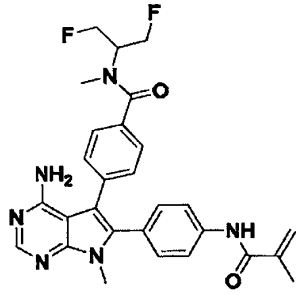
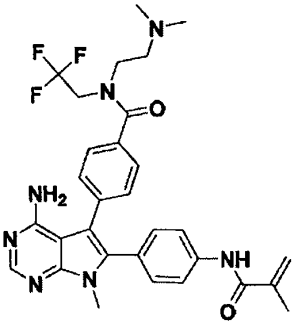
[0978]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1-甲基-2-侧氧基吡咯烷-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.21 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.72 - 7.66 (m, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.27 - 7.21 (m, 2H), 5.93 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 4.57 (q, J = 9.0 Hz, 1H), 3.62 (s, 3H), 3.34 (s, 2H), 2.77 (s, 3H), 2.32 (s, 1H), 1.94 (s, 4H).	524.30
N-(4-(4-氨基-7-甲基-5-(6-(吡咯烷-1-羰基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.31 (dd, J = 1.9, 1.1 Hz, 1H), 8.23 (s, 1H), 7.79 - 7.64 (m, 4H), 7.33 - 7.16 (m, 2H), 6.09 (s, 2H), 5.86 - 5.76 (m, 1H), 5.54 (q, J = 1.5 Hz, 1H), 3.63 (d, J = 10.6 Hz, 5H), 3.52 - 3.42 (m, 2H), 1.95 (t, J = 1.2 Hz, 3H), 1.83 (dqd, J = 5.1, 3.7, 1.7 Hz, 4H).	482.35
(R)-N-(4-(4-氨基-5-(4-(2-(甲氧基甲基)吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.45 (d, J = 7.8 Hz, 2H), 7.26 (dd, J = 8.4, 2.8 Hz, 4H), 5.80 (s, 2H), 5.53 (t, J = 1.5 Hz, 1H), 4.25 (s, 1H), 3.62 (s, 4H), 3.50 - 3.35 (m, 3H), 3.30 (s, 2H), 2.91 (s, 1H), 2.04 - 1.95 (m, 1H), 1.95 (d, J = 1.2 Hz, 3H), 1.85 (s, 2H), 1.70 (s, 1H).	525.40
(S)-N-(4-(4-氨基-5-(4-(2-(甲氧基甲基)吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.26 (dd, J = 8.4, 2.8 Hz, 4H), 5.95 (s, 2H), 5.80 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 4.25 (s, 1H), 4.04 (s, 0H), 3.62 (s, 3H), 3.42 (d, J = 7.1 Hz, 1H), 2.90 (s, 1H), 2.04 - 1.92 (m, 4H), 1.85 (s, 3H), 1.70 (s, 1H).	525.45

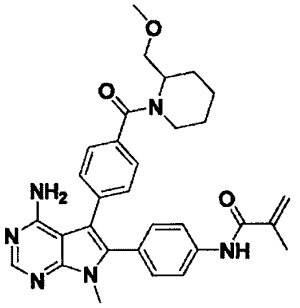
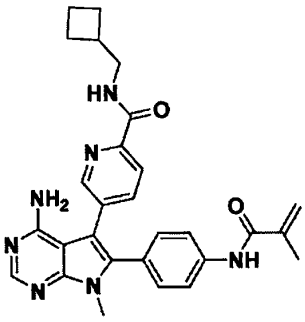
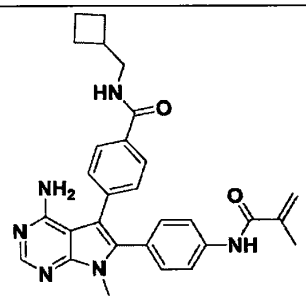
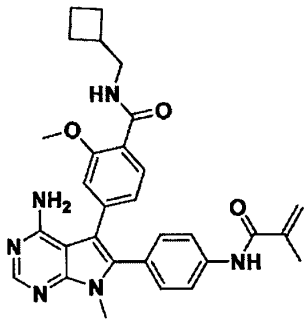
[0979]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-5-(4-(2-氰基吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.74 - 7.68 (m, 2H), 7.57 (d, J = 7.8 Hz, 2H), 7.33 - 7.23 (m, 4H), 5.80 (s, 1H), 5.53 (d, J = 2.0 Hz, 1H), 4.88 (t, J = 6.7 Hz, 1H), 3.70 - 3.60 (m, 4H), 3.59 - 3.50 (m, 1H), 2.33 (s, 1H), 2.18 (dq, J = 12.2, 6.1 Hz, 1H), 2.05 - 1.90 (m, 5H).	506.20
(R)-N-(4-(4-氨基-5-(4-(3-甲氧基哌啶-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.24 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.33 (s, 2H), 7.26 (dd, J = 8.3, 6.1 Hz, 4H), 6.14 (s, 2H), 5.79 (s, 1H), 5.53 (d, J = 1.6 Hz, 1H), 3.62 (s, 4H), 3.52 (s, 3H), 3.22 (s, 3H), 2.98 (s, 1H), 1.94 (d, J = 1.5 Hz, 3H), 1.67 (s, 3H), 1.42 (s, 1H).	525.35
(S)-N-(4-(4-氨基-5-(4-(3-甲氧基哌啶-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.30 - 7.22 (m, 4H), 5.95 (s, 0H), 5.79 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 3.97-3.63 (m, 4H), 3.62-3.31 (m, 3H), 3.29-3.13 (m, 3H), 2.98 (s, 1H), 1.94 (t, J = 1.3 Hz, 3H), 1.85 (s, 1H), 1.67 (s, 1H), 1.57 (s, 1H), 1.41 (s, 1H).	525.45
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-甲氧基-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.19 (d, J = 14.1 Hz, 2H), 7.75 - 7.69 (m, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.34 - 7.26 (m, 2H), 6.93 (d, J = 1.5 Hz, 1H), 6.86 (dd, J = 7.8, 1.5 Hz, 1H), 6.02 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 4.43 (d, J = 7.0 Hz, 1H), 3.82 (td, J = 10.2, 9.7, 6.7 Hz, 2H), 3.71 (s, 3H), 3.71 (td, J = 8.2, 5.6 Hz, 1H), 3.60 (s, 3H), 3.55 (dd, J = 8.9, 4.0 Hz, 1H), 2.15 (dq, J = 12.6, 7.6 Hz, 1H), 1.95 (d, J = 1.2 Hz, 3H), 1.89 - 1.80 (m, 1H).	527.30

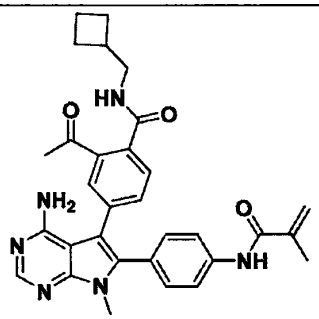
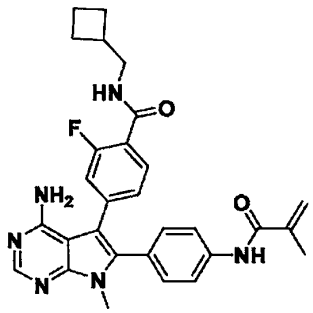
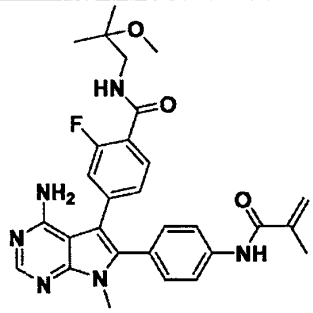
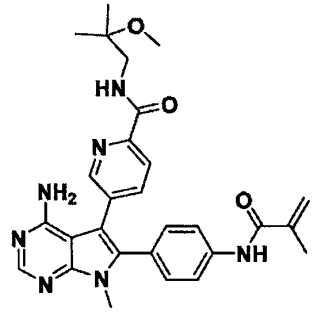
[0980]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-(氧杂环丁-3-基)-7H-吡咯并[2,3-d]嘧啶-5-基)-2-甲氧基-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.24 - 8.15 (m, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 6.93 (s, 1H), 6.84 (d, J = 7.9 Hz, 1H), 5.80 (s, 1H), 5.59 - 5.51 (m, 2H), 5.15 (t, J = 6.8 Hz, 2H), 4.60 (t, J = 6.9 Hz, 2H), 4.42 (s, 1H), 3.81 (td, J = 10.1, 9.6, 6.5 Hz, 2H), 3.70 (s, 4H), 3.54 (dd, J = 8.8, 4.0 Hz, 1H), 2.14 (dq, J = 14.6, 7.6 Hz, 1H), 1.95 (s, 3H), 1.84 (s, 1H).	569.40
N-(4-(4-氨基-5-(4-(2-氰基吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 7.7 Hz, 2H), 7.28 (dd, J = 13.0, 8.2 Hz, 4H), 5.80 (s, 1H), 5.53 (s, 1H), 4.87 (s, 1H), 3.61 (s, 3H), 3.55 (s, 1H), 2.22 - 2.14 (m, 1H), 1.94 (d, J = 1.5 Hz, 3H).	506.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(1,3-二氟丙-2-基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.22 (s, 1H), 7.74 - 7.67 (m, 2H), 7.37 (s, 1H), 7.27 (dd, J = 8.7, 6.8 Hz, 5H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 4.95 - 4.30 (dd, J = 8.7, 6.8 Hz, 5H), 3.62 (s, 3H), 2.96 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	519.4
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-(二甲基氨基)乙基)-N-(2,2,2-三氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.41 (s, 1H), 7.56 (dd, J = 7.5, 5.7 Hz, 3H), 7.41 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.26 - 7.18 (m, 2H), 5.83 (d, J = 1.2 Hz, 1H), 5.52 (d, J = 1.6 Hz, 1H), 4.26 (s, 2H), 3.74 (s, 3H), 3.61 (s, 2H), 2.46 (s, 2H), 2.24 - 2.05 (m, 9H).	580.3

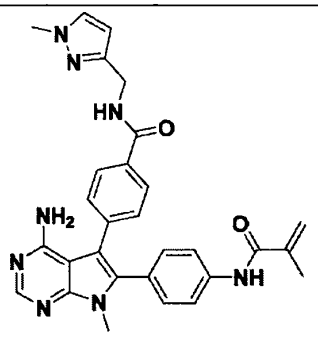
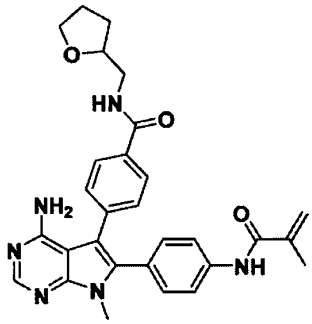
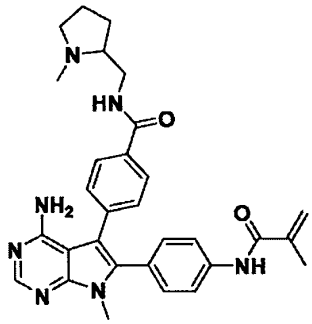
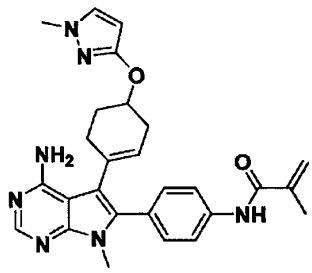
[0981]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-(2-(甲氧基甲基)哌啶-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.73 - 7.66 (m, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.29 - 7.22 (m, 4H), 5.94 (s, 2H), 5.79 (s, 1H), 5.53 (d, J = 1.9 Hz, 1H), 3.61 (s, 3H), 3.32 (s, 4H), 2.94 (s, 1H), 1.94 (t, J = 1.2 Hz, 3H), 1.57 (s, 4H), 1.38 (s, 1H).	539.25
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丁基甲基)吡啶酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.73 (t, J = 6.2 Hz, 1H), 8.33 (d, J = 2.1 Hz, 1H), 8.23 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.0, 2.2 Hz, 1H), 7.76 - 7.69 (m, 2H), 7.30 - 7.24 (m, 2H), 6.13 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.61 (s, 3H), 3.32 (d, J = 13.5 Hz, 1H), 2.55 (d, J = 7.4 Hz, 1H), 2.01 - 1.90 (m, 1H), 1.95 (s, 4H), 1.88 - 1.76 (m, 2H), 1.76 - 1.64 (m, 2H).	496.30
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丁基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.42 (t, J = 5.8 Hz, 1H), 8.21 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.28 (dd, J = 10.3, 8.3 Hz, 4H), 5.91 -5.80 (s, 2H), 5.53 (s, 1H), 3.61 (s, 3H), 3.28 (t, J = 6.4 Hz, 3H), 2.05 - 1.94 (m, 1H), 1.99 (s, 2H), 1.95 (s, 2H), 1.82 (p, J = 7.2, 6.3 Hz, 2H), 1.71 (p, J = 8.6, 7.8 Hz, 2H).	495.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丁基甲基)-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.21 (s, 1H), 8.07 (t, J = 5.8 Hz, 1H), 7.75 - 7.69 (m, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.34 - 7.27 (m, 2H), 6.93 (d, J = 1.5 Hz, 1H), 6.86 (dd, J = 7.9, 1.5 Hz, 1H), 6.01 (s, 1H), 5.81 (s, 1H), 5.54 (s, 1H), 3.72 (s, 3H), 3.34 - 3.26 (m, 5H), 2.00 (dd, J = 8.5, 3.9 Hz, 1H), 1.96 (s, 4H), 1.90 - 1.78 (m, 2H), 1.1-1.73 (ddd, J = 17.0, 8.4, 4.5 Hz, 3H).	525.30

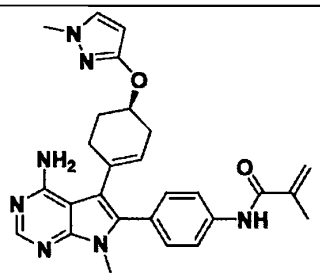
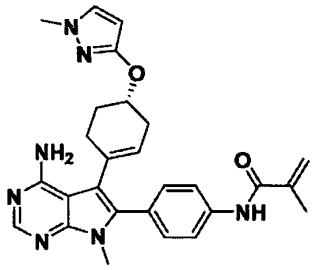
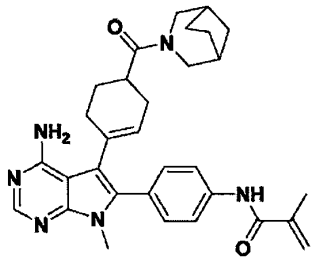
[0982]

化合物	结构	质子 NMR	MS [M+1]
2-乙酰基-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丁基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.75 - 7.67 (m, 2H), 7.51 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 1.4 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.24 (dd, J = 7.7, 1.5 Hz, 1H), 6.20 (s, 1H), 5.79 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.61 (s, 3H), 3.45 (dd, J = 14.0, 7.6 Hz, 1H), 3.38 - 3.28 (m, 1H), 2.74 (q, J = 7.6 Hz, 1H), 2.03 - 1.97 (m, 1H), 1.98 (s, 1H), 1.95 (t, J = 1.2 Hz, 3H), 1.84 - 1.72 (m, 4H), 1.51 (s, 3H).	537.4
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丁基甲基)-2-氟苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.25 (dt, J = 6.0, 2.9 Hz, 1H), 8.22 (s, 1H), 7.78 - 7.70 (m, 2H), 7.54 (t, J = 7.8 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.10 (dd, J = 7.9, 1.6 Hz, 1H), 7.06 (dd, J = 11.4, 1.6 Hz, 1H), 5.81 (s, 1H), 5.54 (t, J = 1.5 Hz, 1H), 3.59 (s, 3H), 3.27 (dd, J = 7.0, 5.8 Hz, 2H), 2.48 (s, 1H), 2.04 - 1.92 (m, 5H), 1.89 - 1.77 (m, 2H), 1.80 - 1.65 (m, 2H).	513.2
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟-N-(2-甲氧基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.21 (s, 1H), 8.00 (q, J = 4.3, 2.8 Hz, 1H), 7.76 - 7.69 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.12 - 7.03 (m, 2H), 5.80 (t, J = 1.0 Hz, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.59 (s, 3H), 3.31 (d, J = 6.0 Hz, 2H), 3.13 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H), 1.12 (s, 6H).	531.3
5-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基-2-甲基丙基)吡啶酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.37 (d, J = 2.1 Hz, 1H), 8.30 (t, J = 6.2 Hz, 1H), 8.22 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.81 - 7.69 (m, 3H), 7.30 - 7.24 (m, 2H), 6.12 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 3.36 (d, J = 6.2 Hz, 2H), 3.15 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H), 1.11 (s, 6H).	514.40

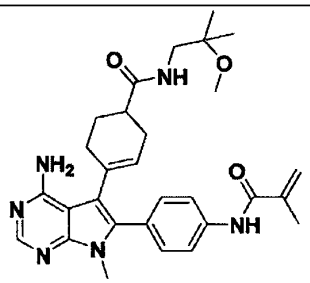
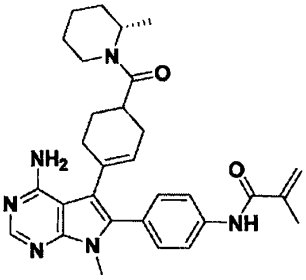
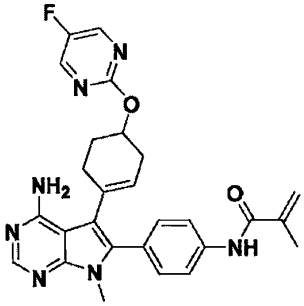
[0983]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-甲基-1H-吡唑-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.86 (t, J = 5.9 Hz, 1H), 8.21 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 2.2 Hz, 1H), 7.32 - 7.23 (m, 4H), 6.12 (d, J = 2.2 Hz, 1H), 5.91 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 4.39 (d, J = 5.8 Hz, 2H), 3.78 (s, 3H), 3.61 (s, 3H), 1.95 (s, 3H), 1.29 (s, 1H).	521.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((四氢呋喃-2-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.50 (t, J = 5.9 Hz, 1H), 8.22 (s, 1H), 7.84 - 7.77 (m, 2H), 7.74 - 7.66 (m, 2H), 7.32 - 7.23 (m, 4H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.97 (p, J = 6.3 Hz, 1H), 3.82 - 3.73 (m, 1H), 3.67 - 3.57 (m, 1H), 3.62 (s, 3H), 3.25 (s, 2H), 1.95 (t, J = 1.2 Hz, 3H), 1.94 - 1.85 (m, 1H), 1.85 - 1.77 (m, 2H), 1.65 - 1.54 (m, 1H).	511.3
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-甲基吡咯烷-2-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 7.82 - 7.75 (m, 2H), 7.74 - 7.66 (m, 2H), 7.33 - 7.23 (m, 4H), 5.80 (d, J = 1.4 Hz, 1H), 5.56 - 5.51 (m, 1H), 3.61 (s, 3H), 3.46 (dt, J = 12.9, 5.0 Hz, 1H), 3.16 (s, 1H), 2.97 (s, 1H), 2.34 (s, 4H), 2.17 (s, 1H), 1.95 (t, J = 1.2 Hz, 3H), 1.85 (s, 1H), 1.63 (s, 3H).	524.3
N-(4-(4-氨基-7-甲基-5-(4-(1-甲基-1H-吡唑-3-基氧基)环己-1-烯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.13 (s, 1H), 7.85 - 7.79 (m, 2H), 7.49 - 7.42 (m, 3H), 5.83 (s, 1H), 5.68 (dd, J = 11.6, 3.0 Hz, 2H), 5.58 - 5.53 (m, 1H), 4.83 - 4.74 (m, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 2.55 (s, 1H), 2.33 (d, J = 18.3 Hz, 1H), 2.16 - 2.06 (m, 1H), 2.01 - 1.91 (m, 4H), 1.89 (q, J = 6.4 Hz, 1H), 1.80 (d, J = 9.1 Hz, 1H).	484.4

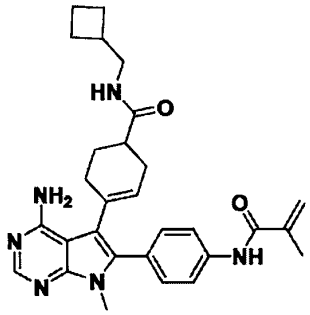
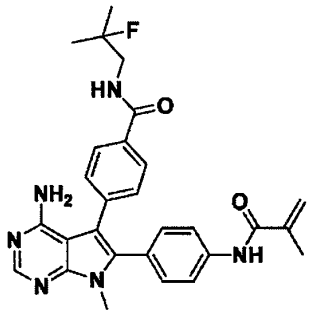
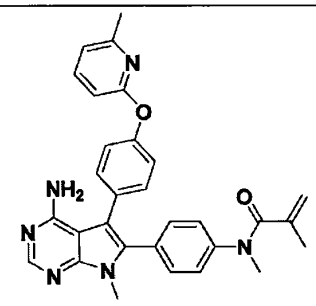
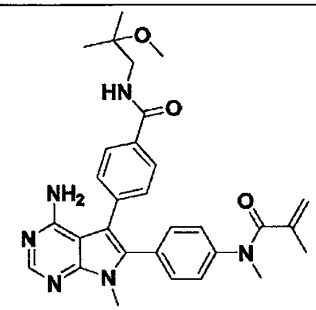
[0984]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-7-甲基-5-(4-(1-甲基-1H-吡唑-3-基氧基)环己-1-烯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.13 (s, 1H), 7.86 - 7.79 (m, 2H), 7.50 - 7.42 (m, 3H), 5.83 (d, J = 1.4 Hz, 1H), 5.72 - 5.64 (m, 2H), 5.56 (t, J = 1.5 Hz, 1H), 4.78 (q, J = 2.7 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 2.55 (d, J = 8.1 Hz, 1H), 2.33 (d, J = 18.2 Hz, 1H), 2.18 - 2.06 (m, 1H), 2.03 - 1.93 (m, 4H), 1.89 (q, J = 6.3 Hz, 1H), 1.83 - 1.73 (m, 1H).	484.3
(S)-N-(4-(4-氨基-7-甲基-5-(4-(1-甲基-1H-吡唑-3-基氧基)环己-1-烯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.13 (s, 1H), 7.86 - 7.79 (m, 2H), 7.49 - 7.42 (m, 3H), 5.83 (s, 1H), 5.71 - 5.64 (m, 2H), 5.56 (t, J = 1.5 Hz, 1H), 4.81 - 4.75 (m, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 2.52 (s, 1H), 2.33 (d, J = 18.3 Hz, 1H), 2.12 (d, J = 17.4 Hz, 1H), 2.04 - 1.93 (m, 4H), 1.88 (q, J = 6.3 Hz, 1H), 1.80 (d, J = 8.6 Hz, 1H).	484.3
N-(4-(5-(4-(3-氮杂双环[3.2.1]辛烷-3-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.09 (s, 1H), 7.90 - 7.76 (m, 2H), 7.43 (d, J = 8.2 Hz, 2H), 6.52 (s, 2H), 5.83 (s, 1H), 5.75 (s, 1H), 5.55 (s, 1H), 4.17 (d, J = 12.6 Hz, 1H), 4.08 (d, J = 12.8 Hz, 0H), 3.73 (s, 1H), 3.58 (s, 3H), 3.14 - 3.02 (m, 2H), 2.57 (d, J = 12.0 Hz, 1H), 2.19 (s, 4H), 1.97 (s, 3H), 1.86 (s, 1H), 1.65 (s, 1H), 1.54 (s, 7H), 1.30 (s, 1H), 1.24 (s, 1H).	525.35

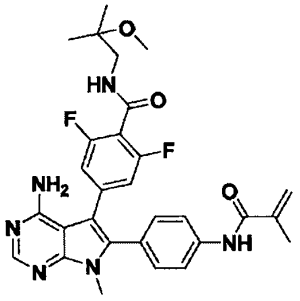
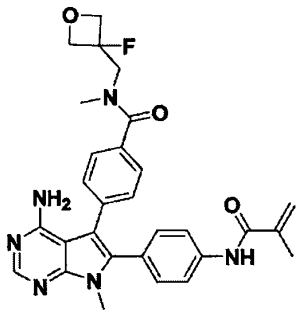
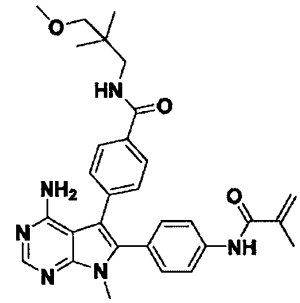
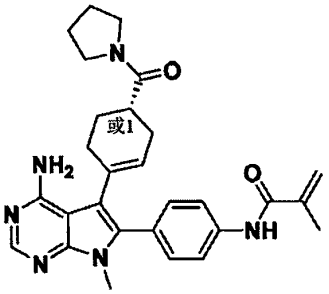
[0985]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基-2-甲基丙基)环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 7.90 (t, J = 6.1 Hz, 1H), 7.88 - 7.82 (m, 2H), 7.51 - 7.44 (m, 2H), 5.89 (s, 1H), 5.84 (s, 1H), 5.57 (d, J = 1.9 Hz, 1H), 3.67 (s, 3H), 3.25 (dd, J = 13.6, 6.8 Hz, 1H), 3.08 (s, 3H), 3.01 (dd, J = 13.6, 5.3 Hz, 1H), 2.74 (d, J = 4.7 Hz, 1H), 2.28 (s, 1H), 1.98 (d, J = 1.1 Hz, 3H), 1.92 (d, J = 12.0 Hz, 1H), 1.80 (d, J = 12.8 Hz, 2H), 1.66 (d, J = 11.7 Hz, 1H), 1.03 (d, J = 5.3 Hz, 6H).	517.25
N-(4-(4-氨基-7-甲基-5-(4-((S)-2-甲基哌啶-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (d, J = 1.8 Hz, 1H), 8.10 (s, 1H), 7.84 - 7.77 (m, 2H), 7.46 - 7.40 (m, 2H), 6.54 (s, 2H), 5.83 (s, 1H), 5.80 - 5.73 (m, 1H), 5.55 (d, J = 2.0 Hz, 1H), 4.76 (s, 1H), 4.31 (s, 1H), 3.75 (d, J = 12.4 Hz, 1H), 3.58 (s, 3H), 3.07 (s, 1H), 3.01 (s, 1H), 2.60 (s,2H), 2.31 (s, 1H), 2.23 (s, 2H), 2.08 (s, 1H), 1.98 (d, J = 1.5 Hz, 4H), 1.91 (s, 1H), 1.81 (d, J = 17.7 Hz, 1H), 1.60 (s, 6H), 1.51 (d, J = 14.5 Hz, 1H), 1.20 (s, 2H), 1.08 - 0.98 (m, 2H).	513.35
N-(4-(4-氨基-5-(4-(5-氟嘧啶-2-基氧基)环己-1-烯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.68 (s, 2H), 8.13 (s, 1H), 7.87 - 7.79 (m, 2H), 7.50 - 7.42 (m, 2H), 5.83 (t, J = 1.0 Hz, 1H), 5.74 - 5.67 (m, 1H), 5.55 (t, J = 1.5 Hz, 1H), 5.24 - 5.18 (m, 1H), 3.58 (s, 3H), 2.67 - 2.63 (s, 1H), 2.40 (s, 1H), 2.13 - 2.02 (m, 2H), 1.98 (t, J = 1.2 Hz, 3H), 1.93 - 1.83 (m, 2H).	500.2

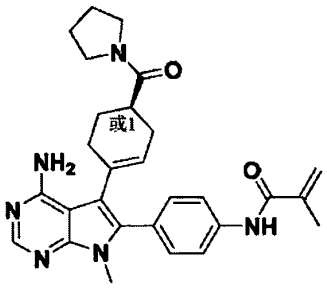
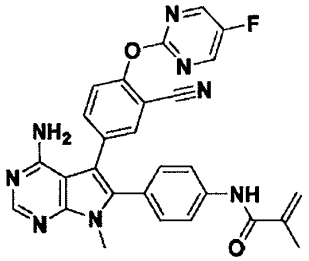
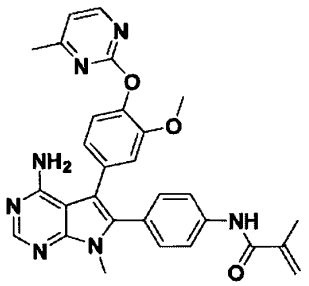
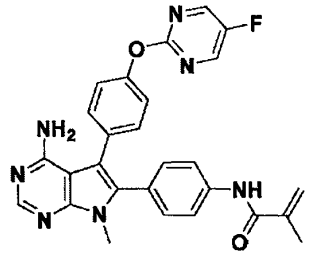
[0986]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丁基甲基)环己-3-烯-1-甲酰胺		3[1]H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.10 (s, 1H), 7.85 - 7.77 (m, 3H), 7.46 - 7.39 (m, 2H), 6.45 (s, 2H), 5.83 (s, 1H), 5.81 - 5.75 (m, 1H), 5.58 - 5.53 (m, 1H), 3.57 (s, 3H), 3.13 (dt, J = 13.0, 6.4 Hz, 1H), 3.02 (dt, J = 13.0, 6.0 Hz, 1H), 2.47 (t, J = 5.9 Hz, 1H), 2.43 - 2.33 (m, 1H), 2.35 - 2.26 (m, 1H), 2.22 (d, J = 5.3 Hz, 1H), 1.98 (d, J = 1.2 Hz, 3H), 1.98 - 1.86 (m, 4H), 1.85 - 1.70 (m, 2H), 1.68 - 1.55 (m, 4H). (m, 1H)	499.30
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-氟-2-甲基丙基)苯甲酰胺		[1]H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.59 (t, J = 6.3 Hz, 1H), 8.21 (s, 1H), 7.96 - 7.79 (m, 2H), 7.76 - 7.60 (m, 2H), 7.43 - 6.93 (m, 4H), 5.79 (s, 1H), 5.53 (d, J = 1.8 Hz, 1H), 3.61 (s, 3H), 3.49 (d, J = 6.2 Hz, 1H), 3.44 (d, J = 6.2 Hz, 1H), 1.94 (t, J = 1.3 Hz, 3H), 1.35 (s, 3H), 1.29 (s, 3H).	501.30
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-N-甲基甲基丙烯酰胺		[1]H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.79 - 7.69 (m, 1H), 7.39 - 7.32 (m, 2H), 7.32 - 7.26 (m, 2H), 7.26 - 7.19 (m, 2H), 7.13 - 7.05 (m, 2H), 7.02 (d, J = 7.3 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 5.93 (s, 2H), 5.04 (p, J = 1.6 Hz, 1H), 4.86 (t, J = 1.3 Hz, 1H), 3.62 (s, 3H), 3.27 (s, 3H), 2.35 (s, 3H), 1.69 (d, J = 1.3 Hz, 3H).	505.25
4-(4-氨基-7-甲基-6-(4-(N-甲基甲基丙烯酰胺基)苯基)-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基-2-甲基丙基)苯甲酰胺		[1]H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 2H), 7.86 - 7.76 (m, 2H), 7.39 - 7.19 (m, 6H), 5.95 (s, 2H), 5.09 - 5.04 (m, 1H), 4.86 (s, 1H), 3.62 (s, 3H), 3.34 (s, 2H), 3.27 (s, 3H), 3.15 (s, 3H), 1.70 (d, J = 1.5 Hz, 3H), 1.11 (s, 6H).	527.25

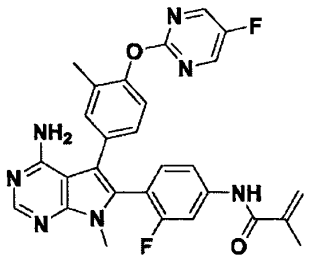
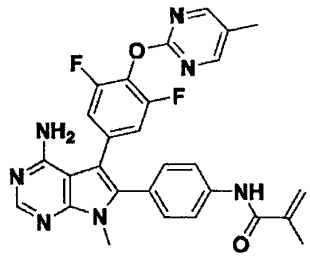
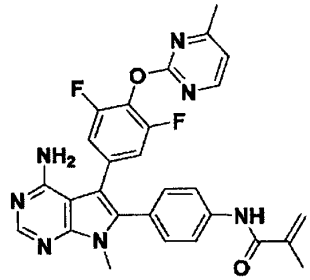
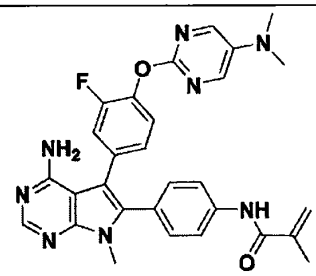
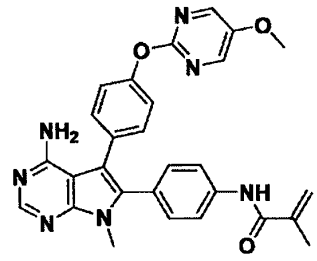
[0987]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2,6-二氟-N-(2-甲氧基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.50 (t, J = 6.1 Hz, 1H), 8.22 (s, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.38 - 7.28 (m, 2H), 6.94 (d, J = 8.1 Hz, 2H), 6.08 (s, 2H), 5.82 (s, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 3.30 (d, J = 6.2 Hz, 2H), 3.12 (s, 3H), 1.96 (d, J = 1.2 Hz, 3H), 1.12 (s, 6H).	549.45
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((3-氟氧杂环丁-3-基)甲基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.21 (s, 1H), 7.77 - 7.65 (m, 2H), 7.37 (d, J = 7.8 Hz, 2H), 7.33 - 7.21 (m, 4H), 5.95 (s, 1H), 5.80 (t, J = 1.1 Hz, 1H), 5.53 (t, J = 1.5 Hz, 1H), 4.66 (d, J = 20.1 Hz, 4H), 4.06 (d, J = 22.7 Hz, 2H), 3.62 (s, 3H), 2.97 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	529.30
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3-甲氧基-2,2-二甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (d, J = 12.8 Hz, 2H), 7.88 - 7.71 (m, 2H), 7.74 - 7.50 (m, 2H), 7.40 - 6.99 (m, 4H), 5.79 (s, 3H), 5.53 (d, J = 1.9 Hz, 1H), 3.61 (s, 3H), 3.32 (s, 3H), 3.26 (s, 2H), 3.17 (d, J = 6.3 Hz, 2H), 1.94 (d, J = 1.5 Hz, 3H), 0.86 (s, 6H).	527.30
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.10 (s, 1H), 7.84 - 7.77 (m, 2H), 7.47 - 7.39 (m, 2H), 6.51 (s, 2H), 5.83 (s, 1H), 5.77 (s, 1H), 5.55 (d, J = 1.9 Hz, 1H), 3.58 (s, 3H), 3.55 - 3.48 (m, 1H), 3.47 - 3.39 (m, 1H), 3.31 - 3.22 (m, 2H), 2.83 (t, J = 6.0 Hz, 1H), 2.26 (s, 2H), 1.98 (d, J = 1.3 Hz, 3H), 1.88 (dd, J = 13.4, 6.6 Hz, 4H), 1.77 (q, J = 6.7 Hz, 2H), 1.63 (d, J = 6.2 Hz, 2H).	485.25

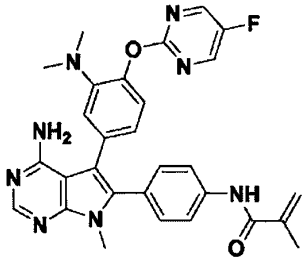
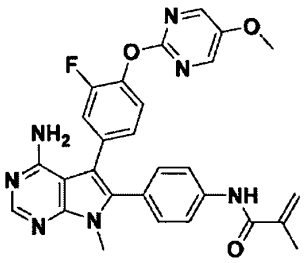
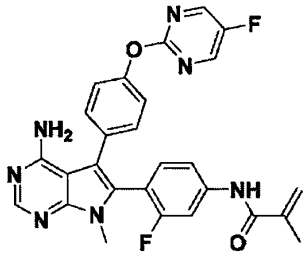
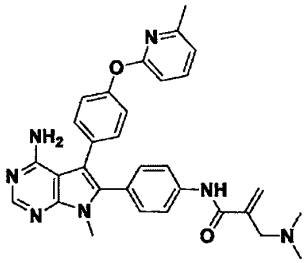
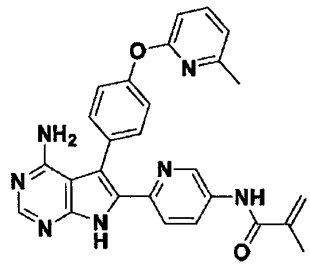
[0988]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.10 (s, 1H), 7.84 - 7.77 (m, 2H), 7.47 - 7.39 (m, 2H), 6.51 (s, 2H), 5.83 (s, 1H), 5.77 (s, 1H), 5.55 (d, J = 1.9 Hz, 1H), 3.58 (s, 3H), 3.55 - 3.48 (m, 1H), 3.47 - 3.39 (m, 1H), 3.31 - 3.22 (m, 2H), 2.83 (t, J = 6.0 Hz, 1H), 2.26 (s, 2H), 1.98 (d, J = 1.3 Hz, 3H), 1.88 (dd, J = 13.4, 6.6 Hz, 4H), 1.77 (q, J = 6.7 Hz, 2H), 1.63 (d, J = 6.2 Hz, 2H).	485.25
N-(4-(4-氨基-5-(3-氰基-4-((5-氟嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.83 (s, 2H), 8.22 (s, 1H), 7.77 (d, J = 1.9 Hz, 1H), 7.76 - 7.73 (m, 2H), 7.55 - 7.53 (m, 1H), 7.45 (s, 1H), 7.33 (d, J = 8.6 Hz, 2H), 6.05 (s, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 3.59 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	521.20
N-(4-(4-氨基-5-(3-甲氧基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.41 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.75 (d, 2H), 7.35 (d, 2H), 7.16 - 7.07 (m, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.1, 1.9 Hz, 1H), 5.96 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.61 (s, 3H), 3.55 (s, 3H), 2.40 (s, 3H), 1.96 (s, 3H).	528.20
N-(4-(4-氨基-5-(4-((5-氟嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.76 (s, 2H), 8.20 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.32 - 7.29 (m, 3H), 7.21 (d, J = 8.7 Hz, 2H), 5.80 (t, J = 1.1 Hz, 2H), 5.54 (t, J = 1.5 Hz, 1H), 3.60 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	496.15

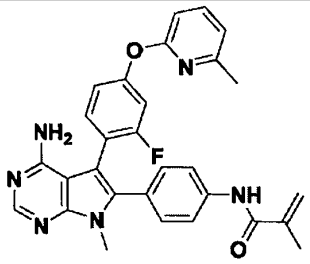
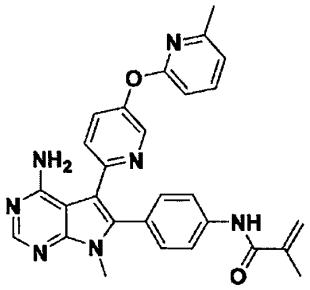
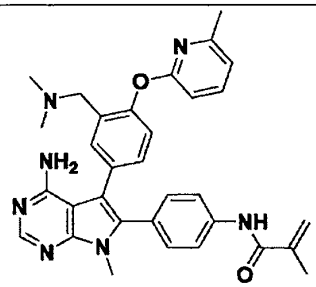
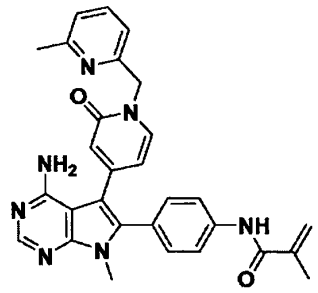
[0989]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((5-氟嘧啶-2-基)氧基)-3-甲基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.73 (s, 2H), 8.22 (s, 1H), 7.79 (dd, J = 12.4, 2.0 Hz, 1H), 7.53 (dd, J = 8.4, 2.0 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.11 (d, J = 2.3 Hz, 2H), 5.83 (s, 1H), 5.59 (s, 1H), 3.53 (s, 3H), 2.06 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	528.35
N-(4-(4-氨基-5-(3,5-二氟-4-((5-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.54 (s, 2H), 8.22 (s, 1H), 7.82 - 7.76 (m, 2H), 7.39 - 7.33 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 6.12 (s, 2H), 5.83 (s, 1H), 5.56 (s, 1H), 3.58 (s, 3H), 2.24 (s, 3H), 1.97 (d, J = 1.2 Hz, 3H).	528.15
N-(4-(4-氨基-5-(3,5-二氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.34 (d, 2H), 7.24 (d, J = 5.0 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.12 (s, 2H), 5.82 (s, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 2.44 (s, 3H), 1.96 (d, J = 1.2 Hz, 3H).	520.25
N-(4-(4-氨基-5-(4-((5-(二甲基氨基)嘧啶-2-基)氧基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.20 (d, J = 9.0 Hz, 3H), 7.87 - 7.65 (m, 2H), 7.45 - 7.24 (m, 3H), 7.21 - 7.03 (m, 2H), 5.68 (d, J = 108.0 Hz, 2H), 3.59 (s, 3H), 2.89 (s, 6H), 1.96 (s, 3H).	539.30
N-(4-(4-氨基-5-(4-((5-甲氧基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.91 (s, 1H), 8.43 (s, 2H), 8.20 (s, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.34 - 7.25 (m, 4H), 7.19 - 7.12 (m, 2H), 5.80 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 3.86 (s, 3H), 3.60 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	508.20

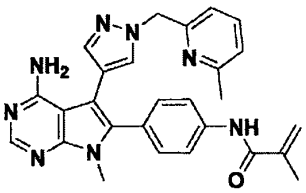
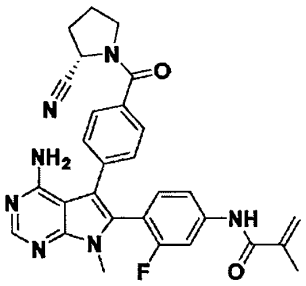
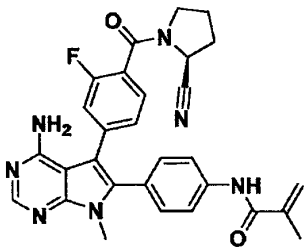
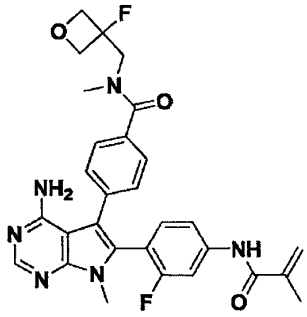
[0990]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-(二甲基氨基)-4-((5-氟嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.72 (s, 2H), 8.20 (s, 1H), 7.91 - 7.63 (m, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.16 - 6.99 (m, 1H), 6.86 (s, 2H), 5.81 (s, 1H), 5.55 (d, J = 1.9 Hz, 1H), 3.59 (s, 3H), 2.55 (s, 6H), 1.96 (t, J = 1.2 Hz, 3H).	539.30
N-(4-(4-氨基-5-(3-氟-4-((5-甲氧基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.43 (s, 2H), 8.21 (s, 1H), 7.80 - 7.73 (m, 2H), 7.38 - 7.29 (m, 3H), 7.18 (dd, J = 11.6, 2.0 Hz, 1H), 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 5.99 (s, 2H), 5.81 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 3.86 (s, 3H), 3.59 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	526.20
N-(4-(4-氨基-5-(4-((5-氟嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.76 (s, 2H), 8.22 (s, 1H), 7.82 - 7.73 (m, 1H), 7.56 - 7.49 (m, 1H), 7.36 - 7.24 (m, 3H), 7.24 - 7.19 (m, 2H), 5.83 (s, 1H), 5.59 (d, J = 2.1 Hz, 1H), 3.54 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	514.35
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-((二甲基氨基)甲基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.20 (s, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.66 - 7.62 (m, 2H), 7.35 - 7.29 (m, 2H), 7.28 - 7.23 (m, 2H), 7.13 - 7.06 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.02 (d, J = 1.8 Hz, 3H), 5.58 (d, J = 1.6 Hz, 1H), 3.62 (s, 3H), 3.23 (s, 2H), 2.35 (s, 3H), 2.25 (s, 6H).	534.25
N-(6-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 10.04 (s, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.13 (s, 1H), 7.91 (dd, J = 8.8, 2.5 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.52 - 7.42 (m, 2H), 7.35 - 7.16 (m, 2H), 7.07 (t, J = 7.6 Hz, 2H), 6.88 (d, J = 8.1 Hz, 1H), 5.85 (s, 1H), 5.58 (s, 1H), 2.39 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	478.30

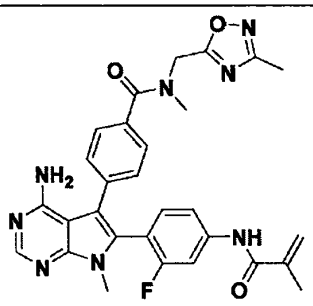
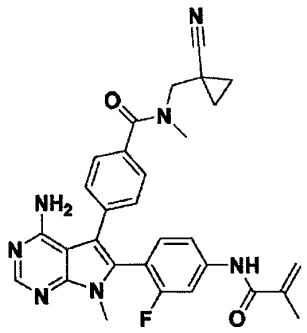
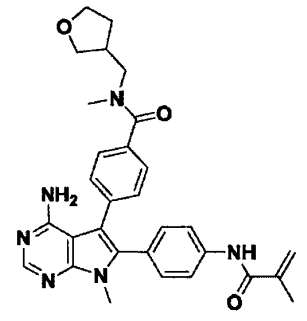
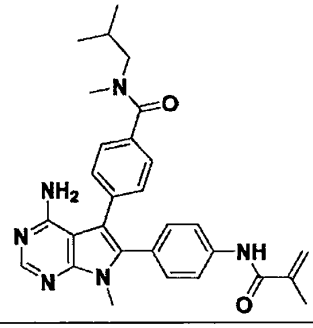
[0991]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(2-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.20 (s, 1H), 7.71 (d, J = 8.7 Hz, 3H), 7.40 - 7.21 (m, 3H), 7.12 - 7.00 (m, 2H), 6.96 (dd, J = 8.4, 2.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 5.80 (s, 3H), 5.53 (t, J = 1.5 Hz, 1H), 3.65 (s, 3H), 2.37 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	509.25
N-(4-(4-氨基-7-甲基-5-(5-((6-甲基吡啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.65 (dd, J = 8.2, 7.3 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.42 - 7.34 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.01 (s, 2H), 6.96 - 6.91 (m, 2H), 6.88 (dd, J = 8.0, 2.0 Hz, 1H), 6.67 - 6.60 (m, 1H), 6.17 (dd, J = 16.8, 2.5 Hz, 1H), 6.08 (d, J = 11.3 Hz, 1H), 5.58 - 5.50 (m, 1H), 3.72 (s, 3H), 3.67(s, 3H), 3.28 (s, 3H), 2.29 (s, 3H).	492.25
N-(4-(4-氨基-5-(3-((二甲基氨基)甲基)-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.76 - 7.66 (m, 3H), 7.35 (d, J = 2.4 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.16 (dd, J = 8.4, 2.4 Hz, 1H), 6.99 (dd, J = 18.4, 7.8 Hz, 2H), 6.71 (d, J = 8.2 Hz, 1H), 5.98 (s, 2H), 5.79 (s, 1H), 5.53 (t, J = 1.6 Hz, 1H), 3.63 (s, 3H), 3.30 (s,2H), 2.31 (s, 3H), 2.00 (s, 6H), 1.95 (t, J = 1.2 Hz, 3H).	548.30
N-(4-(4-氨基-7-甲基-5-(1-((6-甲基吡啶-2-基)甲基)-2-侧氧基-1,2-二氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.22 (s, 1H), 7.85 - 7.76 (m, 2H), 7.69 - 7.61 (m, 2H), 7.39 - 7.31 (m, 2H), 7.15 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 6.32 (s, 2H), 6.21 (d, J = 1.9 Hz, 1H), 6.00 (dd, J = 7.0, 2.0 Hz, 1H), 5.82 (d, J = 1.3 Hz, 1H), 5.55 (d, J = 1.6 Hz, 1H), 5.09 (s, 2H), 3.59 (s, 3H), 2.44 (s, 3H), 1.97 (t, J = 1.2 Hz, 3H).	506.20

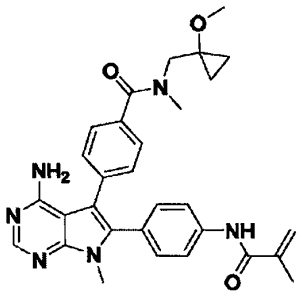
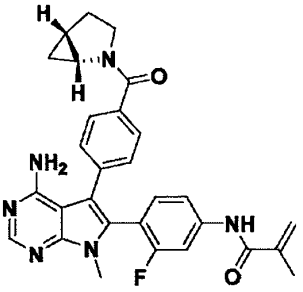
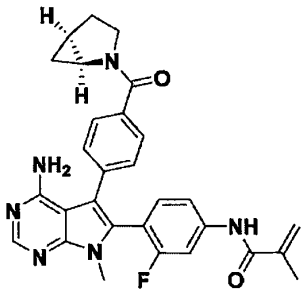
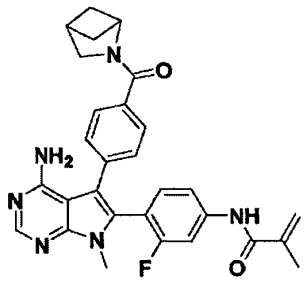
[0992]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-((6-甲基吡啶-2-基)甲基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.18 (s, 1H), 7.84 (s, 1H), 7.80 - 7.72 (m, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.39 - 7.31 (m, 3H), 7.15 (d, J = 7.8 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 6.06 (s, 2H), 5.84 - 5.79 (m, 1H), 5.56 (t, J = 1.4 Hz, 1H), 5.38 (s, 2H), 3.61 (s, 3H), 2.44 (s, 3H), 1.98 (t, J = 1.2 Hz, 3H).	479.35
N-(4-(4-氨基-5-(4-((S)-2-氰基吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.23 (s, 1H), 7.77 (dd, J = 12.5, 2.0 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), 7.32 - 7.22 (m, 3H), 5.82 (t, J = 1.0 Hz, 1H), 5.58 (d, J = 2.0 Hz, 1H), 4.87 (t, J = 6.6 Hz, 1H), 3.65 (s, 1H), 3.56 (s, 4H), 2.32 (s, 1H), 2.17 (ddd, J = 12.7, 11.5, 6.1 Hz, 1H), 1.95 (t, J = 1.3 Hz, 5H).	524.2
(S)-N-(4-(4-氨基-5-(4-(2-氰基吡咯烷-1-羰基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 9.3 Hz, 2H), 5.82 (s, 1H), 5.54 (s, 1H), 4.95 - 4.87 (m, 1H), 3.60 (s, 3H), 1.96 (s, 4H).	524.40
4-(4-氨基-6-(2-氟-4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((3-氟氧杂环丁-3-基)甲基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.22 (s, 1H), 7.76 (dd, J = 12.5, 2.0 Hz, 1H), 7.49 (dd, J = 8.4, 2.0 Hz, 1H), 7.37 (s, 2H), 7.30 - 7.21 (m, 3H), 5.82 (s, 1H), 5.58 (s, 1H), 4.64(s, 5H), 4.09 (s, 1H), 4.03 (s, 1H), 3.55 (s, 3H), 2.96 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	547.30

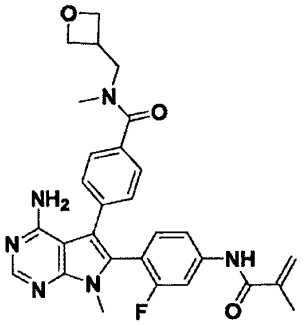
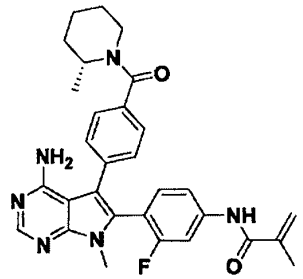
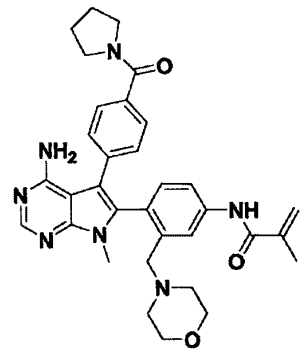
[0993]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(2-氟-4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((3-甲基-1,2,4-恶二唑-5-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.22 (s, 1H), 7.76 (dd, J = 12.4, 2.0 Hz, 1H), 7.48 (dd, J = 8.5, 2.0 Hz, 1H), 7.43 (s, 2H), 7.28 (s, 3H), 7.25 (d, J = 8.5 Hz, 1H), 6.04 (s, 2H), 5.83 (s, 1H), 5.58 (s, 1H), 4.91 (s, 2H), 3.55 (s, 3H), 3.10 (s, 3H), 2.35 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	555.30
4-(4-氨基-6-(2-氟-4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-氰基环丙基)甲基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.23 (s, 1H), 7.77 (dd, J = 12.5, 2.0 Hz, 1H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), 7.37 (d, J = 7.5 Hz, 2H), 7.28 (d, J = 8.2 Hz, 3H), 6.04 (s, 2H), 5.83 (s, 1H), 5.57 (s, 1H), 3.32 (s, 3H), 3.06 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H), 1.29 (s, 2H), 1.16 (t, J = 13.2 Hz, 2H).	538.40
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((四氢呋喃-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.35 (s, 2H), 7.30 - 7.22 (m, 4H), 5.92 (s, 2H), 5.80 (s, 1H), 5.56 - 5.50 (m, 1H), 3.76 (s, 1H), 3.62 (s, 4H), 3.53 (s, 2H), 3.22 (s, 1H), 2.95 (s, 3H), 2.62 (s, 0.5H), 1.95 (d, J = 1.2 Hz, 3H), 1.82 (s, 0.5H), 1.60 (s, 0.5H), 1.31 (s, 0.5H).	525.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-异丁基-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.21 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.35 (s, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.26 (s, 2H), 5.79 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.62 (s, 3H), 3.28 (s, 1H), 3.05 (s, 1H), 2.92 (s, 3H), 2.03 - 1.85 (s, 1H), 1.95 (t, J = 1.2 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.68 (s, 3H).	497.3

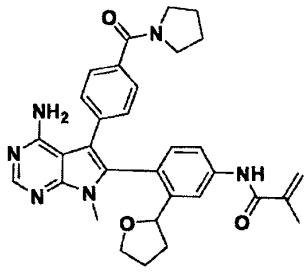
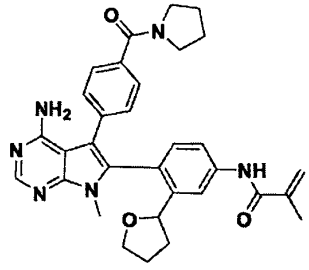
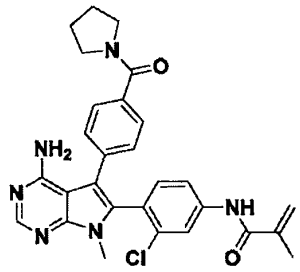
[0994]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-甲氧基环丙基)甲基)-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.23 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.46 - 7.37 (m, 4H), 7.28 (d, J = 7.7 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.83 (s, 1H), 3.71 (s, 3H), 3.59 (s, 1H), 3.39 (s, 2H), 3.11 (s, 3H), 2.86 (s, 1H), 2.04 (d, J = 1.3 Hz, 3H), 0.88 (s, 1H), 0.82 (s, 1H), 0.73 (s, 1H), 0.52 (s, 1H).	525.45
N-(4-(5-(4-((1R,5S)-2-氮杂双环[3.1.0]己烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.23 (s, 1H), 7.77 (dd, J = 12.4, 2.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), 7.28 (d, J = 8.3 Hz, 3H), 6.05 (s, 2H), 5.83 (s, 1H), 5.58 (s, 1H), 3.97 (s, 1H), 3.56 (s, 3H), 3.14 (s, 1H), 2.06 (s, 1H), 1.96 (d, J = 1.2 Hz, 3H), 1.70 (s, 1H), 0.77 (s, 2H).	511.30
N-(4-(5-(4-((1S,5R)-2-氮杂双环[3.1.0]己烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.23 (s, 1H), 7.77 (dd, J = 12.5, 2.0 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.49 (dd, J = 8.4, 2.0 Hz, 2H), 7.28 (d, J = 8.3 Hz, 3H), 6.03 (s, 1H), 5.83 (s, 1H), 5.58 (s, 1H), 3.97 (s, 1H), 3.56 (s, 4H), 3.14 (s, 1H), 2.06 (s, 1H), 1.96 (d, J = 1.2 Hz, 4H), 1.70 (s, 1H), 0.77 (s, 2H).	511.30
N-(4-(5-(4-(2-氮杂双环[2.1.1]己烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.22 (s, 1H), 7.77 (dd, J = 12.5, 2.0 Hz, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.49 (dd, J = 8.4, 2.0 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 7.3 Hz, 3H), 6.02 (s, 1H), 5.83 (s, 1H), 5.57 (s, 1H), 4.33 (d, J = 6.9 Hz, 1H), 3.55 (s, 3H), 3.44 (s, 2H), 2.89 (d, J = 17.1 Hz, 1H), 1.95 (s, 5H), 1.47 (s, 1H), 1.33 (s, 1H).	511.40

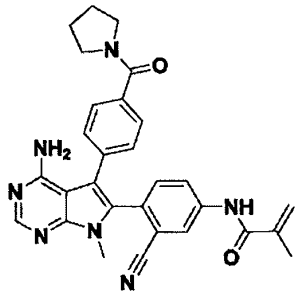
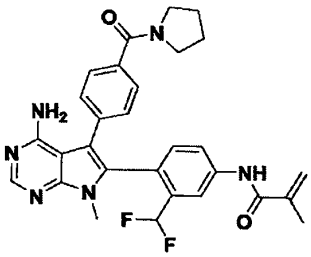
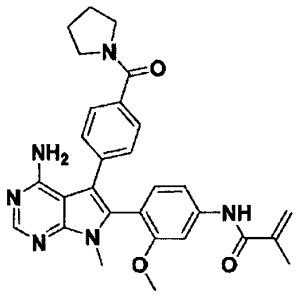
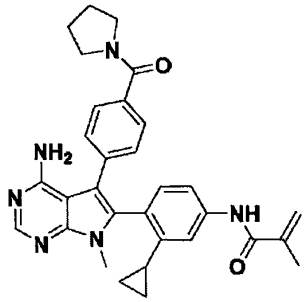
[0995]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(2-氟-4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-(氧杂环丁-3-基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.22 (s, 1H), 7.76 (dd, J = 12.6, 1.9 Hz, 1H), 7.48 (dd, J = 8.4, 2.0 Hz, 1H), 7.34 (d, J = 7.7 Hz, 2H), 7.25 (d, J = 7.8 Hz, 3H), 5.82 (s, 1H), 5.76 (s, 1H), 5.58 (s, 1H), 4.65 (s, 2H), 4.40 (s, 1H), 4.15 (s, 1H), 3.76 (s, 1H), 3.55 (s, 4H), 3.22 (s, 1H), 2.88 (s, 3H), 1.95 (s, 3H).	529.30
(R)-N-(4-(4-氨基-7-甲基-5-(4-(2-甲基哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.22 (s, 1H), 7.76 (dd, J = 12.5, 2.0 Hz, 1H), 7.48 (dd, J = 8.5, 2.0 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.29 - 7.21 (m, 3H), 6.02 (s, 1H), 5.82 (s, 1H), 5.57 (s, 1H), 3.55 (s, 5H), 2.98 (s, 1H), 1.95 (d, J = 1.3 Hz, 3H), 1.64 (d, J = 10.9 Hz, 1H), 1.59 (s, 3H), 1.51 (s, 1H), 1.36 (d, J = 12.8 Hz, 1H), 1.18 (d, J = 6.9 Hz, 3H).	527.40
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(N-吗啉基甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 (s, 1H), 7.80 (dd, J = 8.3, 2.2 Hz, 1H), 7.75 (d, J = 2.2 Hz, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 6.02 (s, 2H), 5.83 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 3.48 - 3.35 (m, 3H), 3.15 (d, J = 13.8 Hz, 1H), 2.75 (d, J = 13.7 Hz, 1H), 2.05 (d, J = 6.7 Hz, 2H), 1.96 (t, J = 1.2 Hz, 5H), 1.83 (dt, J = 19.2, 6.4 Hz, 3H).	580.50

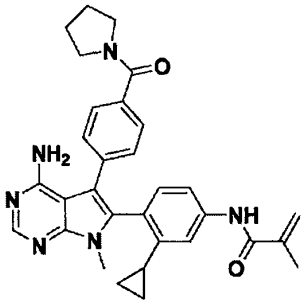
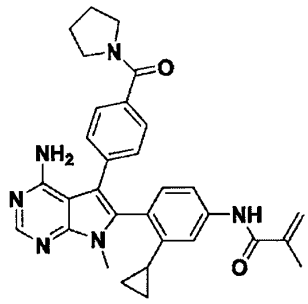
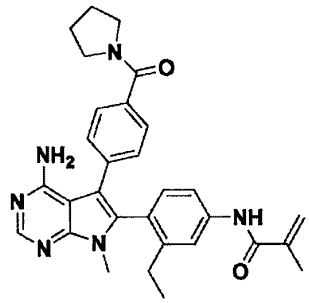
[0996]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(四氢呋喃-2-基)苯基)甲基丙烯酰胺(滞转异构体1)	 滞转异构体 1	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.24 (s, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.74 (dd, J = 8.3, 2.3 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.38 (dd, J = 13.8, 8.2 Hz, 3H), 5.86 - 5.81 (m, 1H), 5.55 (d, J = 1.8 Hz, 1H), 4.47 (dd, J = 7.9, 6.8 Hz, 1H), 4.05 (q, J = 7.2 Hz, 1H), 3.75 (q, J = 7.6 Hz, 1H), 3.59 (t, J = 7.0 Hz, 2H), 3.55 (s, 3H), 3.47 (t, J = 6.6 Hz, 2H), 2.08 - 2.01 (m, 3H), 1.96 (dq, J = 27.5, 6.8 Hz, 5H), 1.87 - 1.74 (m, 1H), 1.61 (dq, J = 12.7, 7.0 Hz, 1H), 1.34 (dq, J = 12.5, 8.1 Hz, 1H).	551.40
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(四氢呋喃-2-基)苯基)甲基丙烯酰胺(滞转异构体1)	 滞转异构体 2	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.24 (s, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.74 (dd, J = 8.3, 2.3 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.38 (dd, J = 13.8, 8.2 Hz, 3H), 5.86 - 5.81 (m, 1H), 5.55 (d, J = 1.8 Hz, 1H), 4.47 (dd, J = 7.9, 6.8 Hz, 1H), 3.91 (q, J = 7.2 Hz, 1H), 3.75 (q, J = 7.6 Hz, 1H), 3.59 (t, J = 7.0 Hz, 2H), 3.55 (s, 3H), 3.47 (t, J = 6.6 Hz, 2H), 2.08 - 2.01 (m, 3H), 1.96 (dq, J = 27.5, 6.8 Hz, 5H), 1.87 - 1.74 (m, 1H), 1.61 (dq, J = 12.7, 7.0 Hz, 1H), 1.34 (dq, J = 12.5, 8.1 Hz, 1H).	551.40
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氯苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.23 (s, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.65 (dd, J = 8.4, 2.1 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 6.02 (s, 1H), 5.83 (d, J = 1.4 Hz, 1H), 5.58 (s, 1H), 3.48 (s, 3H), 3.42 (dt, J = 18.3, 6.6 Hz, 4H), 1.98 - 1.93 (m, 3H), 1.83 (dt, J = 18.7, 6.6 Hz, 4H).	515.35

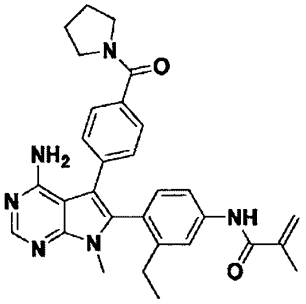
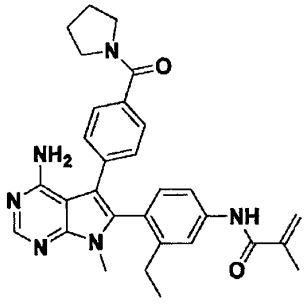
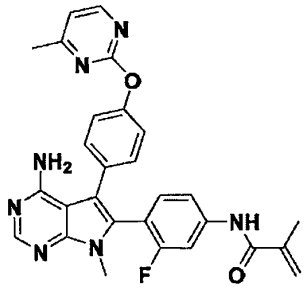
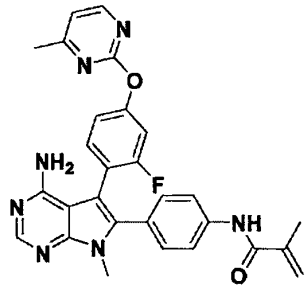
[0997]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氰基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.26 (s, 1H), 8.20 (d, J = 2.2 Hz, 1H), 8.03 (dd, J = 8.6, 2.3 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 6.12 (s, 1H),5.86 (s, 1H), 5.61 (s, 1H), 3.56 (s, 3H), 3.49 - 3.38 (m, 4H), 1.96 (s, 3H), 1.88 - 1.78 (m, 4H).	506.35
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(二氟甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.24 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 8.00 - 7.93 (m, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 6.51 (d, J = 5.6 Hz, 1H), 6.02 (s, 1H), 5.86 (d, J = 1.3 Hz, 1H), 5.58 (d, J = 1.7 Hz, 1H), 3.44 (d, J = 13.6 Hz, 6H), 1.96 (t, J = 1.2 Hz, 3H), 1.82 (dq, J = 19.2, 6.7 Hz, 4H).	531.25
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲氧基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.19 (s, 1H), 7.62 (d, J = 1.9 Hz, 1H), 7.49 - 7.43 (m, 2H), 7.26 (dd, J = 8.3, 1.9 Hz, 1H), 7.25 - 7.18 (m, 2H), 6.99 (d, J = 8.2 Hz, 1H), 5.92 (s, 1H), 5.81 (t, J = 1.0 Hz, 1H), 5.54 (t, J = 1.4 Hz, 1H), 3.70 (s, 3H), 3.47 (s, 4H), 3.45 - 3.37 (m, 3H), 1.96 (t, J = 1.2 Hz, 3H), 1.83 (dt, J = 17.0, 6.4 Hz, 4H).	511.40
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-环丙基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.32 (s, 1H), 7.61 (dd, J = 8.3, 2.1 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.28 - 7.16 (m, 4H), 5.80 (s, 1H), 5.53 (t, J = 1.6 Hz, 1H), 3.52 (s, 3H), 3.43 (dt, J = 17.2, 6.6 Hz, 4H), 1.94 (t, J = 1.2 Hz, 3H), 1.83 (dq, J = 18.6, 6.8 Hz, 4H), 1.52 - 1.40 (m, 1H), 0.84 (ddt, J = 10.2, 8.7, 4.0 Hz, 1H), 0.72 - 0.52 (m, 2H), 0.44 - 0.34 (m, 1H).	521.4

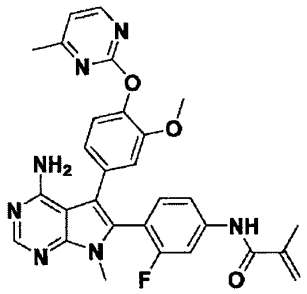
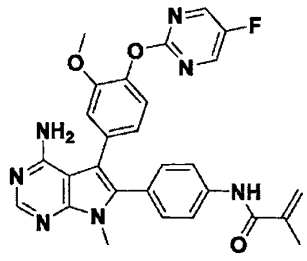
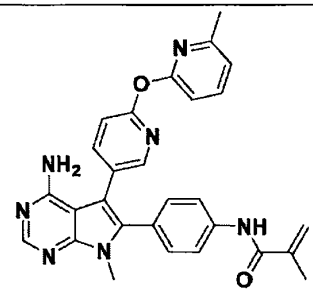
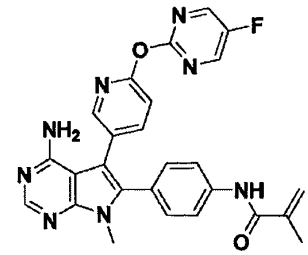
[0998]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-环丙基苯基)甲基丙烯酰胺	 滞转异构体 1	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.29 (s, 1H), 7.60 (dd, J = 8.3, 2.1 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.28 - 7.17 (m, 4H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.52 (s, 3H), 3.43 (dt, J = 17.3, 6.6 Hz, 4H), 1.95 (d, J = 1.2 Hz, 3H), 1.90 - 1.75 (m, 4H), 1.46 (td, J = 8.5, 4.4 Hz, 1H), 0.84 (p, J = 4.9 Hz, 1H), 0.63 (ddt, J = 29.5, 9.2, 4.5 Hz, 2H), 0.39 (p, J = 4.8 Hz, 1H).	521.3
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-环丙基苯基)甲基丙烯酰胺	 滞转异构体 2	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.21 (s, 1H), 7.59 (dd, J = 8.4, 2.1 Hz, 1H), 7.49 - 7.43 (m, 2H), 7.32 - 7.16 (m, 4H), 5.80 (s, 1H), 5.55 - 5.50 (m, 1H), 3.49 (s, 3H), 3.47 - 3.38 (m, 4H), 1.95 (t, J = 1.3 Hz, 3H), 1.83 (dq, J = 17.3, 6.5 Hz, 4H), 1.48 (td, J = 8.3, 4.5 Hz, 1H), 0.85 (s, 1H), 0.66 (d, J = 13.8 Hz, 1H), 0.58 (dt, J = 10.1, 5.2 Hz, 1H), 0.43 - 0.36 (m, 1H).	521.3
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-乙基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.21 (s, 1H), 7.70 - 7.61 (m, 2H), 7.48 - 7.42 (m, 2H), 7.32 (d, J = 8.3 Hz, 1H), 7.26 - 7.19 (m, 2H), 6.19 - 5.79 (m, 3H), 5.53 (t, J = 1.6 Hz, 1H), 3.48 - 3.35 (m, 7H), 2.29 (dt, J = 15.1, 7.4 Hz, 1H), 2.10 (dq, J = 15.0, 7.5 Hz, 1H), 1.96 (t, J = 1.2 Hz, 3H), 1.84 (dq, J = 18.9, 6.8 Hz, 4H), 0.83 (t, J = 7.5 Hz, 3H).	509.3

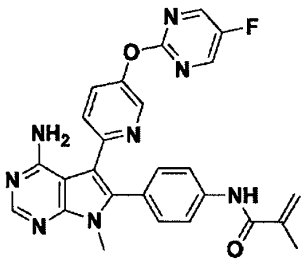
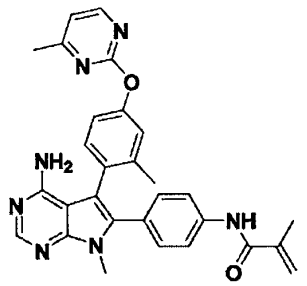
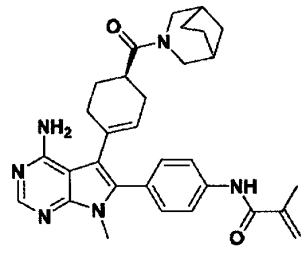
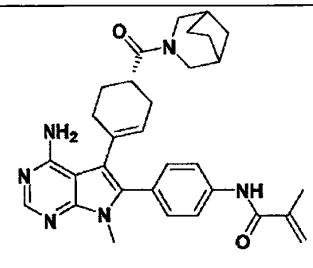
[0999]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-乙基苯基)甲基丙烯酰胺	 滞转异构体 1	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.22 (s, 1H), 7.71 - 7.62 (m, 2H), 7.49 - 7.42 (m, 2H), 7.32 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 5.82 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.48 - 3.35 (m, 7H), 2.30 (dt, J = 15.0, 7.5 Hz, 1H), 2.10 (dq, J = 14.9, 7.5 Hz, 1H), 1.96 (t, J = 1.2 Hz, 3H), 1.85 (dq, J = 18.9, 6.8 Hz, 4H), 0.83 (t, J = 7.5 Hz, 3H).	509.3
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-乙基苯基)甲基丙烯酰胺	 滞转异构体 2	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.22 (s, 1H), 7.71 - 7.62 (m, 2H), 7.49 - 7.42 (m, 2H), 7.32 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 5.82 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.48 - 3.35 (m, 7H), 2.30 (dt, J = 15.0, 7.5 Hz, 1H), 2.10 (dq, J = 14.9, 7.5 Hz, 1H), 1.96 (d, J = 1.2 Hz, 3H), 1.82 (dq, J = 18.6, 6.6 Hz, 4H), 0.83 (t, J = 7.5 Hz, 3H).	509.3
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.80 - 7.76 (m, 1H), 7.53 - 7.51 (m, 1H), 7.36 - 7.26 (m, 3H), 7.23 - 7.13 (m, 3H), 5.82 (s, 1H), 5.58 (d, J = 1.8 Hz, 1H), 3.54 (s, 3H), 2.41 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	510.20
N-(4-(4-氨基-5-(2-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.50 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.76 - 7.66 (m, 2H), 7.38 (t, J = 8.5 Hz, 1H), 7.31 - 7.27 (m, 2H), 7.22 - 7.15 (m, 2H), 7.09 - 7.07 (m, 1H), 5.80 (d, J = 1.3 Hz, 1H), 5.53 (d, J = 1.7 Hz, 1H), 3.64 (s, 3H), 2.43 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	510.20

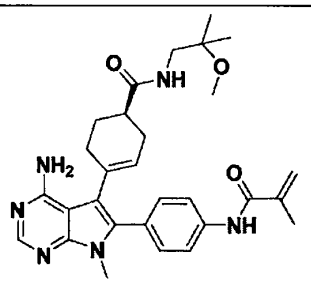
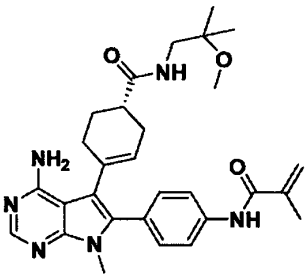
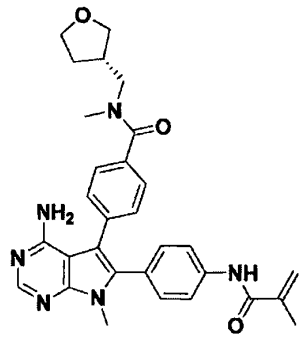
[1000]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-甲氧基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.40 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.80 (dd, J = 12.5, 2.0 Hz, 1H), 7.54 (dd, J = 8.4, 2.0 Hz, 1H), 7.36 (t, J = 8.5 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 5.1 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.1, 2.0 Hz, 1H), 5.83 (s, 1H), 5.58 (s, 1H), 3.55 (d, J = 5.1 Hz, 6H), 2.39 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	540.25
N-(4-(4-氨基-5-(4-((5-氟嘧啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.71 (s, 2H), 8.21 (s, 1H), 7.75 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.1, 2.0 Hz, 1H), 5.81 (s, 1H), 5.54 (s, 1H), 3.60 (s, 3H), 3.56 (s, 3H), 1.96 (d, J = 1.3 Hz, 3H).	526.20
N-(4-(4-氨基-7-甲基-5-(6-((6-甲基吡啶-2-基)氧基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.21 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.75 (t, J = 8.2 Hz, 4H), 7.42 - 7.24 (m, 2H), 7.08 (dd, J = 14.6, 7.9 Hz, 2H), 6.92 (d, J = 8.1 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.61 (s, 3H), 2.38 (s, 3H), 1.96 (t, J = 1.3 Hz, 3H).	492.30
N-(4-(4-氨基-5-(6-((5-氟嘧啶-2-基)氧基)吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.83 (s, 2H), 8.22 (s, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 9.4, 2.5 Hz, 3H), 7.43 - 7.26 (m, 2H), 7.23 (s, 1H), 5.92 (d, J = 81.4 Hz, 3H), 5.55 (d, J = 1.8 Hz, 1H), 3.60 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	497.25

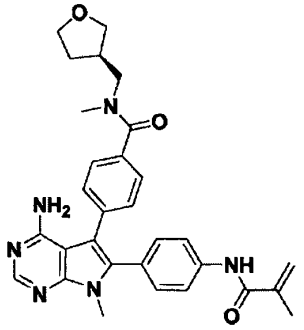
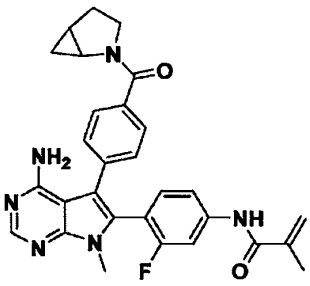
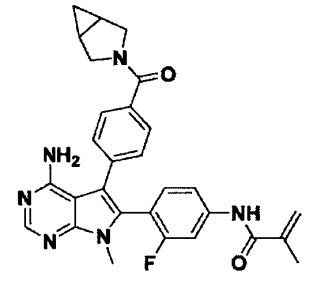
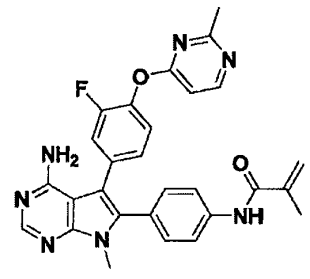
[1001]

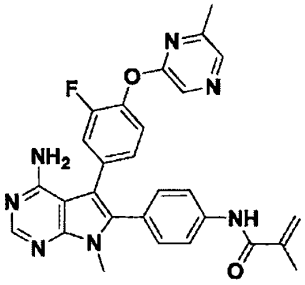
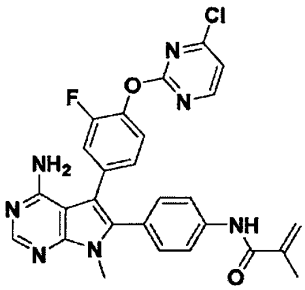
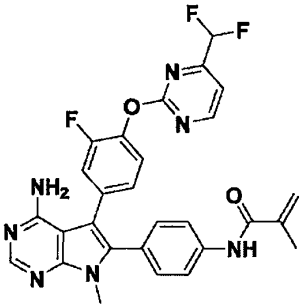
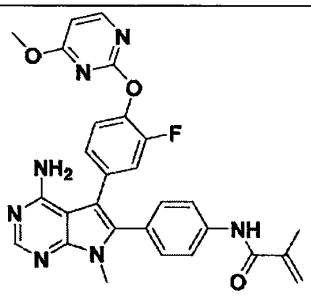
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(5-((5-氟嘧啶-2-基)氧基)吡啶-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.78 (s, 2H), 8.60 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.93 - 7.85 (m, 2H), 7.50 (dd, J = 8.8, 2.8 Hz, 1H), 7.46 - 7.38 (m, 2H), 6.94 (d, J = 8.8 Hz, 1H), 5.84 (t, J = 1.0 Hz, 1H), 5.57 (t, J = 1.6 Hz, 1H), 3.52 (s, 3H), 1.98 (t, J = 1.2 Hz, 3H).	497.30
N-(4-(4-氨基-7-甲基-5-(2-甲基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.19 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.28 (dd, J = 8.6, 2.3 Hz, 3H), 7.15 (d, J = 5.1 Hz, 1H), 7.10 - 7.00 (m, 2H), 5.78 (s, 1H), 5.53 (s, 1H), 3.66 (s, 3H), 2.42 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H).	540.25
N-(4-(5-((4R)-4-(3-氮杂双环[3.2.1]辛烷-3-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.09 (s, 1H), 7.90 - 7.76 (m, 2H), 7.43 (d, J = 8.2 Hz, 2H), 6.52 (s, 2H), 5.83 (s, 1H), 5.75 (s, 1H), 5.55 (s, 1H), 4.17 (d, J = 12.6 Hz, 1H), 4.08 (d, J = 12.8 Hz, 0H), 3.73 (s, 1H), 3.58 (s, 3H), 3.14 - 3.02 (m, 2H), 2.57 (d, J = 12.0 Hz, 1H), 2.19 (s, 4H), 1.97 (s, 3H), 1.86 (s, 1H), 1.65 (s, 1H), 1.54 (s, 7H), 1.30 (s, 1H), 1.24 (s, 1H).	525.30
N-(4-(5-((4S)-4-(3-氮杂双环[3.2.1]辛烷-3-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.09 (s, 1H), 7.90 - 7.76 (m, 2H), 7.43 (d, J = 8.2 Hz, 2H), 6.52 (s, 2H), 5.83 (s, 1H), 5.75 (s, 1H), 5.55 (s, 1H), 4.17 (d, J = 12.6 Hz, 1H), 4.08 (d, J = 12.8 Hz, 0H), 3.73 (s, 1H), 3.58 (s, 3H), 3.14 - 3.02 (m, 2H), 2.57 (d, J = 12.0 Hz, 1H), 2.19 (s, 4H), 1.97 (s, 3H), 1.86 (s, 1H), 1.65 (s, 1H), 1.54 (s, 7H), 1.30 (s, 1H), 1.24 (s, 1H).	525.30

[1002]

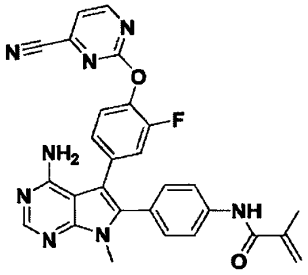
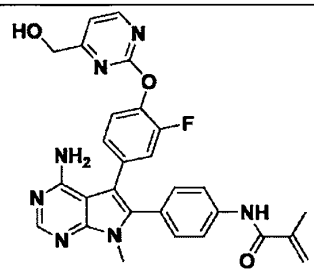
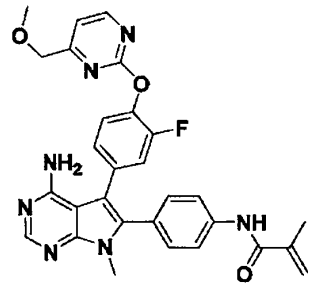
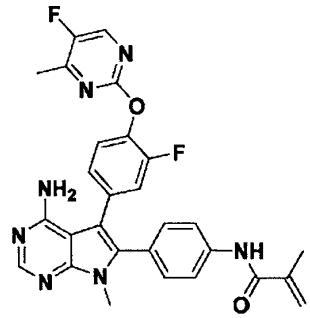
化合物	结构	质子 NMR	MS [M+1]
(R)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基-2-甲基丙基)环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.10 (s, 1H), 7.85 - 7.77 (m, 2H), 7.70 (t, J = 6.2 Hz, 1H), 7.47 - 7.39 (m, 2H), 6.44 (s, 1H), 5.83 (t, J = 1.1 Hz, 1H), 5.78 (s, 1H), 5.58 - 5.53 (m, 1H), 3.57 (s, 3H), 3.19 (dd, J = 13.6, 6.5 Hz, 1H), 3.08 (s, 3H), 3.03 (dd, J = 13.6, 5.6 Hz, 1H), 2.61 (d, J = 6.3 Hz, 1H), 2.29 (s, 1H), 2.21 (d, J = 18.0 Hz, 1H), 1.98 (t, J = 1.2 Hz, 3H), 1.90 (s, 2H), 1.66 (d, J = 6.1 Hz, 2H), 1.03 (d, J = 4.0 Hz, 6H).	517.25
(S)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基-2-甲基丙基)环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.12 (s, 1H), 7.85 - 7.77 (m, 2H), 7.70 (t, J = 6.0 Hz, 1H), 7.47 - 7.39 (m, 2H), 6.50 (s, 1H), 5.86 - 5.76 (m, 2H), 5.55 (t, J = 1.4 Hz, 1H), 3.58 (s, 3H), 3.19 (dd, J = 13.6, 6.5 Hz, 1H), 3.08 (s, 3H), 3.03 (dd, J = 13.6, 5.6 Hz, 1H), 2.65 - 2.58 (m, 1H), 2.26 (d, J = 22.4 Hz, 2H), 1.98 (t, J = 1.2 Hz, 3H), 1.94 - 1.87 (m, 2H), 1.66 (s, 2H), 1.24 (s, 0H), 1.03 (d, J = 4.0 Hz, 6H).	517.30
(S)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((四氢呋喃-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.71 - 7.64 (m, 2H), 7.40 (s, 5H), 7.28 (d, J = 8.2 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.96 - 3.87 (m, 1H), 3.80 (d, J = 7.6 Hz, 2H), 3.71 (s, 3H), 3.60 (d, J = 6.9 Hz, 3H), 3.10 (s, 1H), 3.05 (s, 2H), 2.77 (s, 1H), 2.11 (s, 1H), 2.04 (t, J = 1.3 Hz, 3H), 1.76 (s, 1H).	525.30

[1003]

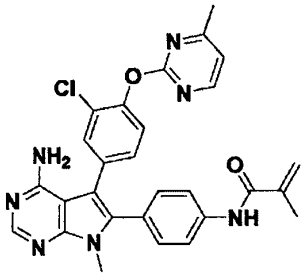
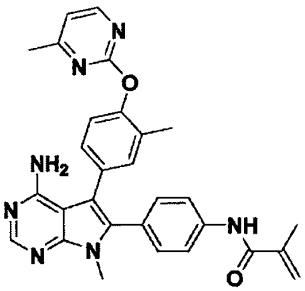
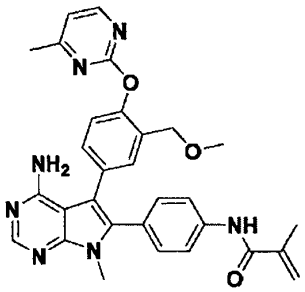
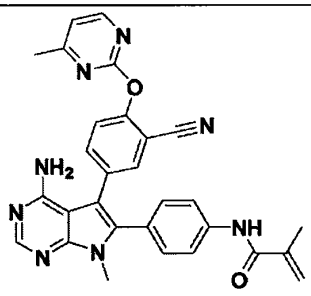
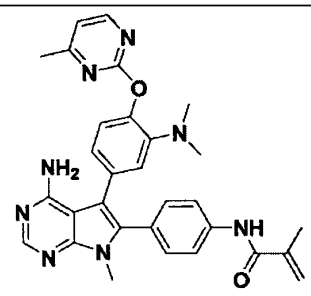
化合物	结构	质子 NMR	MS [M+1]
(R)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((四氢呋喃-3-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.71 - 7.64 (m, 2H), 7.40 (s, 5H), 7.28 (d, J = 8.2 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.96 - 3.87 (m, 1H), 3.80 (d, J = 7.6 Hz, 2H), 3.71 (s, 3H), 3.60 (d, J = 6.9 Hz, 3H), 3.10 (s, 1H), 3.05 (s, 2H), 2.77 (s, 1H), 2.11 (s, 1H), 2.04 (t, J = 1.3 Hz, 3H), 1.76 (s, 1H).	525.30
N-(4-(5-(4-(2-氮杂双环[3.1.0]己烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.22 (s, 1H), 7.76 (dd, J = 12.5, 2.0 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 8.4, 2.1 Hz, 2H), 7.28 (d, J = 8.6 Hz, 3H), 6.03 (s, 1H), 5.82 (d, J = 1.1 Hz, 1H), 5.58 (s, 1H), 3.95 (d, J = 10.7 Hz, 1H), 3.55 (s, 3H), 3.13 (s, 2H), 2.05 (s, 1H), 1.95 (d, J = 1.3 Hz, 4H), 1.69 (s, 4H), 1.59 (s, 1H) , 0.76 (s, 2H).	511.35
N-(4-(5-(4-(3-氮杂双环[3.1.0]己烷-3-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.22 (s, 1H), 7.77 (dd, J = 12.5, 2.0 Hz, 1H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.31 - 7.20 (m, 3H), 5.83 (s, 1H), 5.76 (s, 1H), 5.58 (d, J = 2.0 Hz, 1H), 3.95 (d, J = 11.9 Hz, 1H), 3.66 (d, J = 10.0 Hz, 1H), 3.55 (s, 3H), 3.3 - 3.2 (m, 2H), 1.95 (t, J = 1.2 Hz, 3H), 1.54 (s, 2H), 0.68 - 0.59 (m, 1H), 0.07 (q, J = 4.3 Hz, 1H).	511.30
N-(4-(4-氨基-5-(3-氟-4-((2-甲基嘧啶-4-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.60 (d, J = 5.8 Hz, 1H), 8.21 (s, 1H), 7.78 - 7.72 (m, 2H), 7.35 (t, J = 8.3 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.21 (dd, J = 11.4, 2.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 5.7 Hz, 1H), 6.05 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.62 (s, 3H), 2.46 (s, 3H), 1.95 (s, 3H).	510.20

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((6-甲基吡嗪-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.45 - 8.14 (m, 3H), 7.81 - 7.70 (m, 2H), 7.42 - 7.24 (m, 3H), 7.24 - 7.02 (m, 2H), 6.27 - 5.90 (m, 1H), 5.80 (t, *J* = 1.1 Hz, 1H), 5.54 (t, *J* = 1.5 Hz, 1H), 3.61 (s, 3H), 2.35 (s, 3H), 1.96 (t, *J* = 1.2 Hz, 3H).	510.20
N-(4-(4-氨基-5-(4-((4-氯嘧啶-2-基)氧基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.66 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 5.3 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 13.3 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.21 - 5.90 (m, 1H), 5.5.81 (s, 1H), 5.55 (s, 1H), 3.60 (s, 3H), 1.96 (s, 3H).	530.20
[1004] N-(4-(4-氨基-5-(4-((4-(二氟甲基)嘧啶-2-基)氧基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.90 (d, *J* = 4.9 Hz, 1H), 8.22 (s, 1H), 7.80 - 7.72 (m, 2H), 7.59 (d, *J* = 5.0 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.23 (dd, *J* = 11.4, 2.0 Hz, 1H), 7.15 - 7.06 (m, 1H), 6.88 (d, *J* = 54.0 Hz, 1H), 5.99 (s, 1H), 5.81 (t, *J* = 1.1 Hz, 1H), 5.54 (t, *J* = 1.5 Hz, 1H), 3.60 (s, 3H), 1.96 (t, *J* = 1.2 Hz, 3H).	546.40
N-(4-(4-氨基-5-(3-氟-4-((4-甲氧基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.34 (d, *J* = 5.7 Hz, 1H), 8.21 (s, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.45 - 7.24 (m, 3H), 7.20 (t, *J* = 11.4, 2.0 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 5.7 Hz, 1H), 5.81 (s, 1H), 5.55 (s, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 1.96 (t, *J* = 1.2 Hz, 3H).	526.25

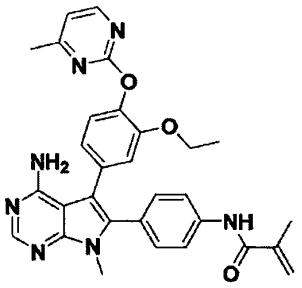
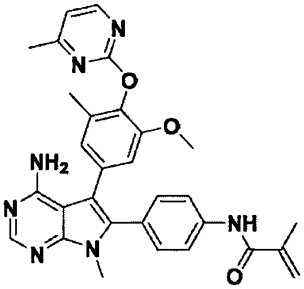
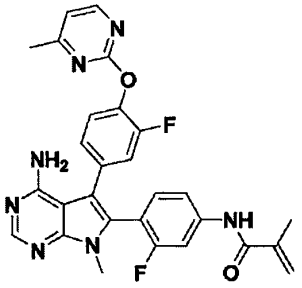
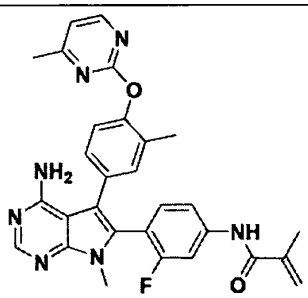
[1005]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((4-氰基嘧啶-2-基)氧基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.03 (d, J = 4.8 Hz, 1H), 8.22 (s, 1H), 7.97 (d, J = 4.8 Hz, 1H), 7.79 - 7.72 (m, 2H), 7.42 (t, J = 8.4 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.25 (dd, J = 11.4, 2.0 Hz, 1H), 7.14 (dd, J = 8.2, 1.8 Hz, 1H), 6.01 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 1.96 (t, J = 1.4 Hz, 3H).	521.25
N-(4-(4-氨基-5-(3-氟-4-((4-(羟基甲基)嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.61 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.80 - 7.72 (m, 2H), 7.34 (dd, J = 8.3, 5.4 Hz, 4H), 7.19 (dd, J = 11.4, 2.0 Hz, 1H), 7.11 (dt, J = 8.3, 1.4 Hz, 1H), 5.84 - 5.79 (m, 1H), 5.67 (t, J = 6.0 Hz, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.50 (d, J = 5.9 Hz, 2H), 3.60 (s, 3H), 3.32 (s, 2H), 1.96 (t, J = 1.2 Hz, 3H).	526.10
N-(4-(4-氨基-5-(3-氟-4-((4-(甲氧基甲基)嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.63 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.79 - 7.73 (m, 2H), 7.41 - 7.31 (m, 2H), 7.32 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 5.0 Hz, 1H), 7.19 (dd, J = 11.4, 2.0 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H), 5.98 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 4.45 (s, 2H), 3.60 (s, 3H), 3.39 (s, 3H), 1.96 (s, 3H).	540.20
N-(4-(4-氨基-5-(3-氟-4-((5-氟-4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.57 (d, J = 1.4 Hz, 1H), 8.21 (s, 1H), 7.80 - 7.71 (m, 2H), 7.41 - 7.30 (m, 3H), 7.20 (dd, J = 11.5, 2.0 Hz, 1H), 7.14 - 7.08 (m, 1H), 5.98 (s, 1H), 5.81 (t, J = 1.1 Hz, 1H), 5.54 (t, J = 1.5 Hz, 1H), 3.60 (s, 3H), 2.43 (d, J = 2.5 Hz, 3H), 1.96 (t, J = 1.2 Hz, 3H).	528.40

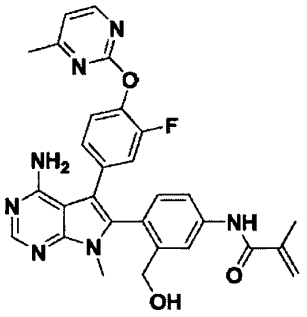
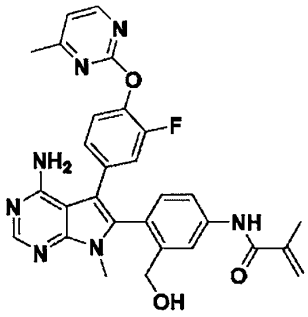
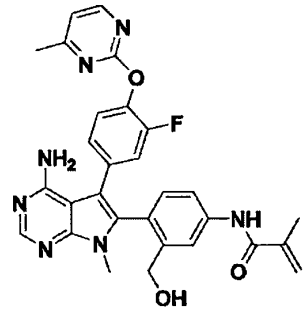
[1006]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氯-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 8.4 Hz, 3H), 7.30 - 7.20 (m, 1H), 7.18 (d, J = 5.0 Hz, 1H), 5.97 (s, 1H), 5.81 (s, 1H), 5.54 (s, 1H), 3.60 (s, 3H), 2.43 (s, 3H), 1.96 (d, J = 1.2 Hz, 3H).	526.15
N-(4-(4-氨基-7-甲基-5-(3-甲基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.44 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 2.0 Hz, 1H), 7.14 - 7.05 (m, 3H), 5.80 (d, J = 1.3 Hz, 2H), 5.54 (s, 1H), 3.60 (s, 3H), 2.41 (s, 3H), 2.04 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H).	506.25
N-(4-(4-氨基-5-(3-(甲氧基甲基)-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.44 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.39 - 7.26 (m, 3H), 7.23 - 7.21 (m, 1H), 7.17 - 7.09 (m, 2H), 5.79 (s, 2H), 5.53 (s, 1H), 4.29 (s, 2H), 3.61 (s, 3H), 3.08 (s, 3H), 2.41 (s, 3H), 1.95 (s, 3H).	536.40
N-(4-(4-氨基-5-(3-氰基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.82 - 7.69 (m, 3H), 7.53 (t, J = 8.6, 2.2 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 5.1 Hz, 1H), 5.81 (s, 1H), 5.55 (s, 1H), 3.60 (s, 3H), 2.45 (s, 3H), 1.96 (t, J = 1.3 Hz, 3H).	517.25
N-(4-(4-氨基-5-(3-(二甲基氨基)-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.43 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.84 - 7.58 (m, 2H), 7.43 - 7.27 (m, 2H), 7.10 (d, J = 5.0 Hz, 1H), 7.05 - 6.97 (m, 1H), 6.83 (d, J = 6.7 Hz, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.60 (s, 3H), 2.55 (s, 6H), 2.40 (s, 3H), 1.96 (s, 3H).	535.45

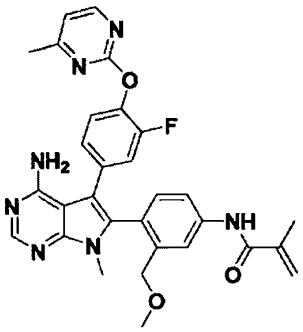
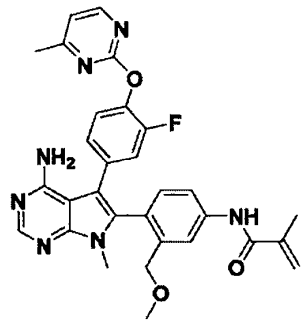
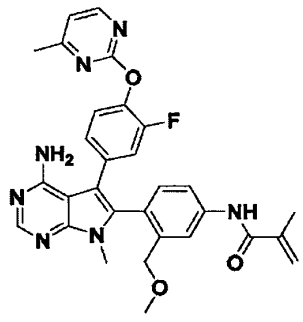
[1007]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-乙氧基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.42 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.18 - 7.05 (m, 2H), 6.94 (d, J = 2.0 Hz, 1H), 6.84 (dd, J = 8.1, 1.9 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 3.81 (d, J = 7.0 Hz, 2H), 3.61 (s, 3H), 2.44 - 2.31 (m, 3H), 1.96 (t, J = 1.3 Hz, 3H), 0.94 (t, J = 6.9 Hz, 3H).	536.45
N-(4-(4-氨基-5-(3-甲氧基-5-甲基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.39 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.87 - 7.69 (m, 2H), 7.43 - 7.30 (m, 2H), 7.09 (d, J = 5.0 Hz, 1H), 6.84 - 6.77 (m, 2H), 5.81 (s, 2H), 5.54 (d, J = 1.5 Hz, 1H), 3.60 (s, 3H), 3.50 (s, 3H), 2.41 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H).	536.45
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.80 (dd, J = 12.5, 2.0 Hz, 1H), 7.55 (dd, J = 8.5, 2.0 Hz, 1H), 7.35 (td, J = 8.4, 2.4 Hz, 2H), 7.22 - 7.16 (m, 2H), 7.13 - 7.08 (m, 1H), 6.07 (s, 2H), 5.83 (s, 1H), 5.59 (s, 1H), 3.54 (s, 3H), 2.42 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	528.35
N-(4-(4-氨基-7-甲基-5-(3-甲基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.44 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.80 (dd, J = 12.4, 1.9 Hz, 1H), 7.53 (dd, J = 8.5, 2.0 Hz, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.23 (s, 1H), 7.14(d, J = 4.0 Hz, 1H), 7.16 - 7.09 (m, 2H), 5.97 (s, 1H), 5.84 (s, 1H), 5.59 (s, 1H), 3.54 (s, 3H), 2.42 (s, 3H), 2.04 (s, 3H), 1.96 (d, J = 1.5 Hz, 3H).	524.35

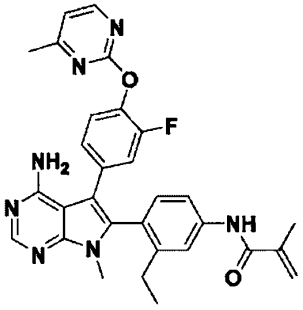
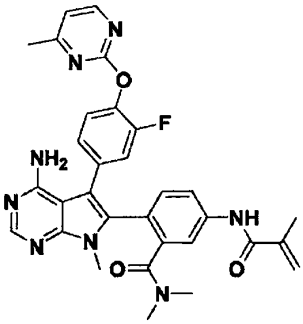
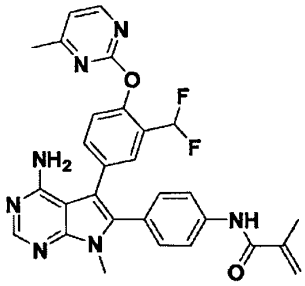
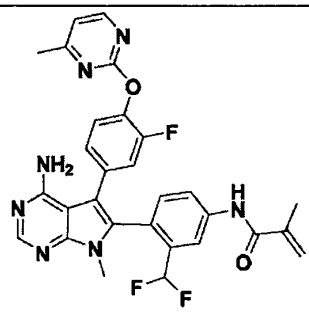
[1008]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(羟基甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.74 (dd, J = 8.3, 2.3 Hz, 1H), 7.36 - 7.27 (m, 2H), 7.20 - 7.11 (m, 2H), 7.08 (dd, J = 8.4, 2.0 Hz, 1H), 6.05 (s, 1H), 5.83 (s, 1H), 5.54 (s, 1H), 5.17 (t, J = 5.3 Hz, 1H), 4.17 (dd, J = 13.9, 5.3 Hz, 1H), 4.02 (dd, J = 13.8, 5.3 Hz, 1H), 2.41 (s, 3H), 1.96 (d, J = 1.6 Hz, 3H).	540.40
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(羟基甲基)苯基)甲基丙烯酰胺 滞转异构体 A		^{1}H NMR (400 MHz, 氯仿-d) δ 8.41 - 8.32 (m, 2H), 7.82 (dd, J = 8.3, 2.2 Hz, 1H), 7.71 - 7.64 (m, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 8.2 Hz, 1H), 7.06 (t, J = 8.2 Hz, 2H), 6.95 (d, J = 5.1 Hz, 1H), 5.85 (s, 1H), 5.60 (s, 1H), 5.54 (d, J = 1.7 Hz, 1H), 4.36 (d, J = 13.2 Hz, 1H), 4.25 (d, J = 13.2 Hz, 1H), 3.59 (s, 3H), 2.51 (s, 3H), 2.13 - 2.08 (m, 3H).	540.40
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(羟基甲基)苯基)甲基丙烯酰胺 滞转异构体 B		^{1}H NMR (400 MHz, 氯仿-d) δ 8.39 (s, 1H), 8.34 (d, J = 5.0 Hz, 1H), 7.82 (dd, J = 8.3, 2.1 Hz, 1H), 7.71 - 7.64 (m, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.21 (t, J = 8.2 Hz, 1H), 7.06 (t, J = 8.0 Hz, 2H), 6.94 (d, J = 5.0 Hz, 1H), 5.85 (s, 1H), 5.53 (d, J = 1.6 Hz, 2H), 4.36 (d, J = 13.3 Hz, 1H), 4.25 (d, J = 13.3 Hz, 1H), 3.59 (s, 3H), 2.51 (s, 3H), 2.10 (t, J = 1.2 Hz, 3H).	540.45

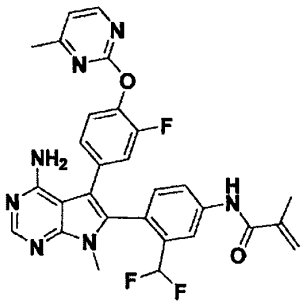
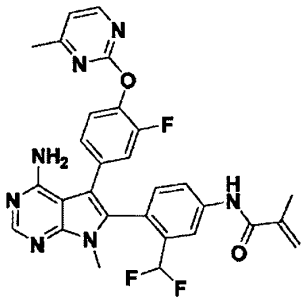
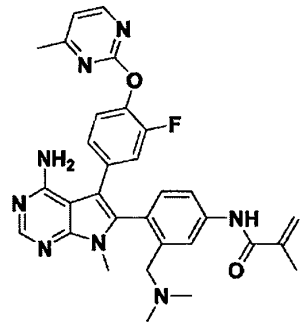
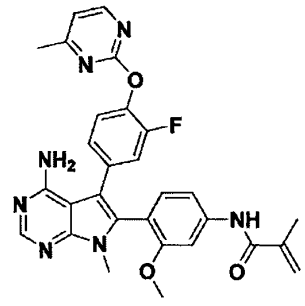
[1009]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(甲氧基甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.86 - 7.76 (m, 2H), 7.38 (d, J = 8.3 Hz, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.20 - 7.10 (m, 2H), 7.07 (dd, J = 8.3, 2.2 Hz, 1H), 6.06 (s, 1H), 5.84 (t, J = 1.1 Hz, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.12 (d, J = 12.7 Hz, 1H), 3.91 (d, J = 12.7 Hz, 1H), 3.42 (s, 3H), 3.10 (s, 3H), 2.40 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	554.25
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(甲氧基甲基)苯基)甲基丙烯酰胺	 滞转异构体 A	^{1}H NMR (400 MHz, 氯仿-d) δ 8.41 (s, 1H), 8.35 (d, J = 5.0 Hz, 1H), 7.89 - 7.82 (m, 1H), 7.64 - 7.56 (m, 2H), 7.32 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 8.2 Hz, 1H), 7.06 (d, J = 10.7 Hz, 2H), 6.94 (d, J = 5.0 Hz, 1H), 5.84 (s, 1H), 5.53 (s, 1H), 5.37 (s, 1H), 4.14 (d, J = 12.4 Hz, 1H), 3.99 (d, J = 12.3 Hz, 1H), 3.57 (s, 3H), 3.21 (s, 3H), 2.50 (s, 3H), 2.10 (t, J = 1.2 Hz, 3H).	554.45
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(甲氧基甲基)苯基)甲基丙烯酰胺	 滞转异构体 B	^{1}H NMR (400 MHz, 氯仿-d) δ 8.41 (s, 1H), 8.35 (d, J = 5.0 Hz, 1H), 7.85 (dd, J = 8.3, 2.2 Hz, 1H), 7.64 - 7.56 (m, 2H), 7.32 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 8.2 Hz, 1H), 7.10 - 7.03 (m, 2H), 6.94 (d, J = 5.0 Hz, 1H), 5.84 (s, 1H), 5.53 (d, J = 1.5 Hz, 1H), 5.40 (s, 2H), 4.14 (d, J = 12.4 Hz, 1H), 3.99 (d, J = 12.4 Hz, 1H), 3.57 (s, 3H), 3.21 (s, 3H), 2.50 (s, 3H), 2.13 - 2.08 (m, 3H).	554.45

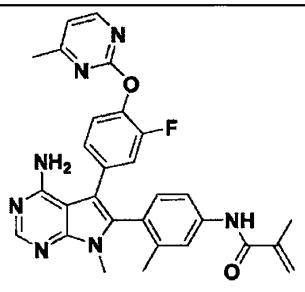
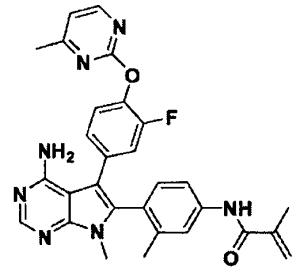
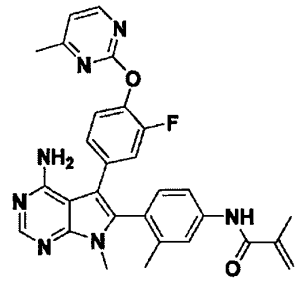
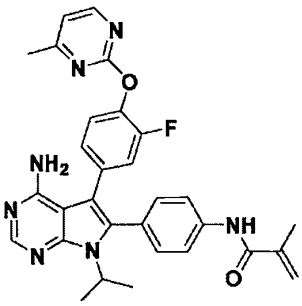
[1010]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-(4-甲基嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-乙基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 7.70 (d, J = 6.2 Hz, 2H), 7.39 - 7.28 (m, 2H), 7.18 (d, J = 5.1 Hz, 1H), 7.13 (d, J = 11.3 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 5.82 (s, 1H), 5.54 (s, 1H), 2.40 (s, 3H), 2.17 (dd, J = 14.9, 7.2 Hz, 1H), 1.97 (s, 3H), 0.90 (t, J = 7.6 Hz, 3H).	538.25
2-(4-氨基-5-(3-氟-4-(4-甲基嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-5-甲基丙烯酰胺基-N,N-二甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.85 (dd, J = 8.5, 2.3 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.12 - 7.05 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 5.85 (d, J = 1.2 Hz, 1H), 5.57 (d, J = 1.8 Hz, 1H), 3.45 (s, 3H), 2.71 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	581.3
N-(4-(4-氨基-5-(3-(二氟甲基)-4-(4-甲基嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.43 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.58 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.00 - 6.71 (m, 1H), 5.83 (s, 1H), 5.55 (s, 1H), 3.72 (s, 3H), 2.51 (s, 3H), 2.05 (s, 3H).	542.2
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(二氟甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 8.13 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.22 - 7.14 (m, 2H), 7.07 (dd, J = 8.3, 2.1 Hz, 1H), 6.58 (s, 1H), 6.06 (s, 1H), 5.86 (s, 1H), 5.58 (d, J = 1.8 Hz, 1H), 3.42 (s, 3H), 2.40 (s, 3H), 1.97 (d, J = 1.2 Hz, 3H).	560.40

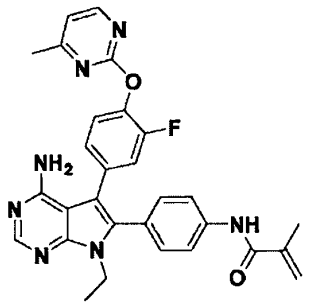
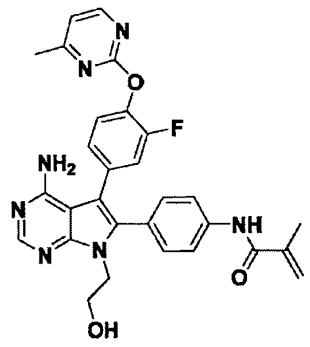
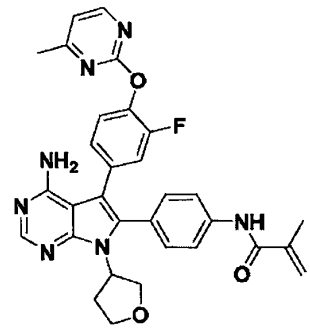
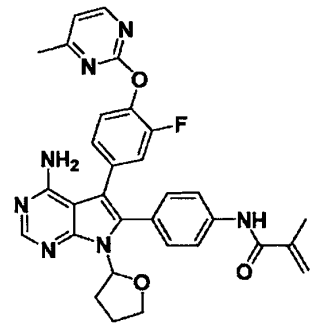
[1011]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(二氟甲基)苯基)甲基丙烯酰胺	 滞转异构体 A	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.43 (s, 1H), 8.36 (d, *J* = 5.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.71 (s, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.23 (t, *J* = 8.2 Hz, 1H), 7.09 - 7.00 (m, 2H), 6.94 (d, *J* = 5.0 Hz, 1H), 6.31 (s, 1H), 5.87 (s, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 5.29 (s, 2H), 3.57 (s, 3H), 2.50 (s, 3H), 2.11 (dd, *J* = 1.6, 0.9 Hz, 3H).	560.35
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-(二氟甲基)苯基)甲基丙烯酰胺	 滞转异构体 B	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.42 (s, 1H), 8.36 (d, *J* = 5.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.72 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 8.3 Hz, 1H), 7.09 - 7.00 (m, 2H), 6.94 (d, *J* = 5.0 Hz, 1H), 6.31 (s, 1H), 5.87 (s, 1H), 5.56 (q, *J* = 1.6 Hz, 1H), 5.40 (s, 2H), 3.58 (s, 3H), 2.50 (s, 3H), 2.11 (d, *J* = 1.3 Hz, 3H).	560.40
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-((二甲基氨基)甲基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.45 (d, *J* = 5.0 Hz, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 7.86 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 5.0 Hz, 1H), 7.11 (d, *J* = 11.5 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.07 (s, 2H), 5.84 (s, 1H), 5.53 (s, 1H), 3.4 (d, *J* = 14.1 Hz, 3H), 3.15 (d, *J* = 14.1 Hz, 1H), 2.79 (d, *J* = 14.0 Hz, 1H), 2.39 (s, 3H), 1.95 (d, *J* = 5.1 Hz, 9H).	567.30
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲氧基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.20 (s, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.38 - 7.27 (m, 2H), 7.18 (d, *J* = 5.0 Hz, 1H), 7.15 - 7.08 (m, 2H), 7.08 - 7.01 (m, 1H), 6.00 (s, 2H), 5.82 (s, 1H), 5.55 (s, 1H), 3.71 (s, 3H), 3.47 (s, 3H), 2.41 (s, 3H), 1.96 (t, *J* = 1.2 Hz, 3H).	540.25

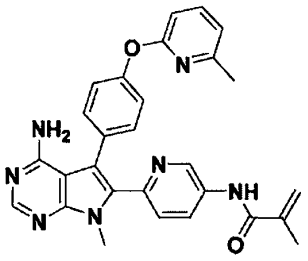
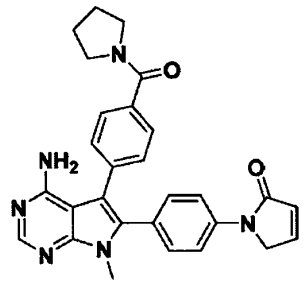
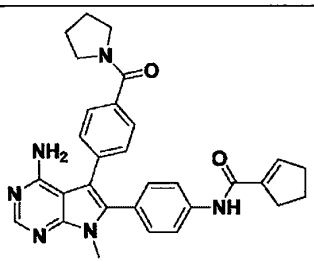
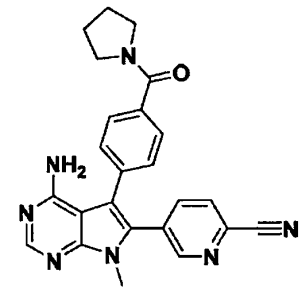
[1012]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.69 - 7.59 (m, 2H), 7.36 - 7.27 (m, 2H), 7.18 (d, J = 5.1 Hz, 1H), 7.12 (dd, J = 11.5, 2.1 Hz, 1H), 7.06 (dd, J = 8.4, 2.1 Hz, 1H), 6.04 (s, 2H), 5.81 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 3.43 (s, 3H), 2.41 (s, 3H), 1.96 (d, J = 1.4 Hz, 6H).	524.25
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺 滞转异构体 A		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.69 - 7.60 (m, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.18 (d, J = 5.0 Hz, 1H), 7.15 - 7.09 (m, 1H), 7.06 (d, J = 8.6 Hz, 1H), 5.81 (s, 2H), 5.53 (s, 1H), 3.43 (s, 3H), 2.41 (s, 3H), 1.96 (s, 6H).	524.25
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺 滞转异构体 B		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 7.69 - 7.60 (m, 2H), 7.32 (dd, J = 8.5, 7.1 Hz, 2H), 7.18 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 12.5 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 5.81 (s, 2H), 5.53 (s, 1H), 3.43 (s, 3H), 2.41 (s, 3H), 1.96 (s, 6H).	524.25
N-(4-(4-氨基-5-(3-氟-4-(4-甲基嘧啶-2-基氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.19 (s, 1H), 7.80 - 7.73 (m, 2H), 7.35 - 7.27 (m, 3H), 7.23 - 7.15 (m, 2H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 5.81 (s, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.33 (p, J = 6.8 Hz, 1H), 2.41 (s, 3H), 1.96 (t, J = 1.3 Hz, 3H), 1.59 (d, J = 6.8 Hz, 6H).	538.2

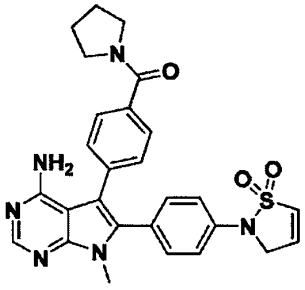
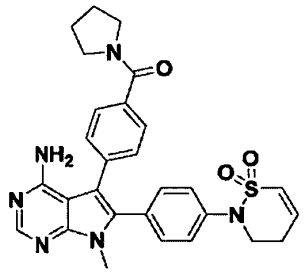
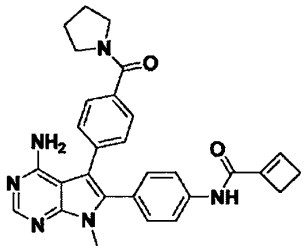
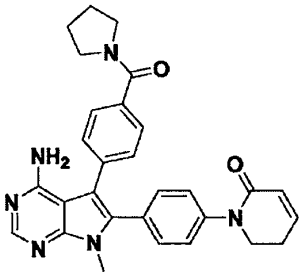
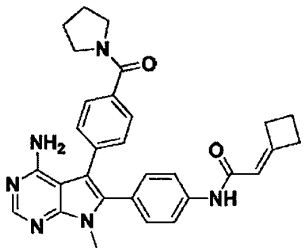
[1013]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-乙基-5-(3-氟-4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.81 - 7.74 (m, 2H), 7.38 - 7.28 (m, 3H), 7.23 - 7.15 (m, 2H), 7.11 (dd, J = 8.3, 2.1 Hz, 1H), 5.81 (s, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 2.42 (s, 3H), 1.96 (d, J = 1.4 Hz, 3H), 1.22 - 1.10 (m, 3H).	524.4
N-(4-(4-氨基-5-(3-氟-4-(4-甲基嘧啶-2-基氧基)苯基)-7-(2-羟乙基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.79 - 7.72 (m, 2H), 7.37 (s, 1H), 7.39 - 7.29 (m, 2H), 7.21 - 7.13 (m, 2H), 7.10 (dd, J = 8.1, 2.0 Hz, 1H), 5.99 (s, 2H), 5.81 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 4.90 (t, J = 5.5 Hz, 1H), 4.11 (t, J = 6.6 Hz, 2H), 3.58 (t, J = 6.2 Hz, 2H), 2.42 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	540.40
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-(四氢呋喃-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.32 (dd, J = 8.5, 3.5 Hz, 3H), 7.24 - 7.15 (m, 2H), 7.11 (dd, J = 8.2, 2.0 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 4.75 - 4.62 (m, 1H), 4.18 (dt, J = 14.4, 8.0 Hz, 2H), 3.96 (t, J = 8.2 Hz, 1H), 3.83 (q, J = 7.3 Hz, 1H), 2.77 (dq, J = 14.1, 7.3 Hz, 1H), 2.41 (s, 3H), 2.24 - 2.11 (m, 1H), 1.96 (s, 3H).	566.45
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-(四氢呋喃-2-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.21 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.6 Hz, 3H), 7.25 - 7.15 (m, 2H), 7.11 (d, J = 8.2 Hz, 1H), 5.94 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 4.09 (d, J = 7.7 Hz, 1H), 3.78 (s, 1H), 2.81 (s, 1H), 2.41 (s, 3H), 2.20 (d, J = 29.2 Hz, 2H), 1.95 (s, 3H), 1.89 (s, 1H).	566.45

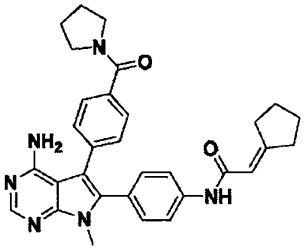
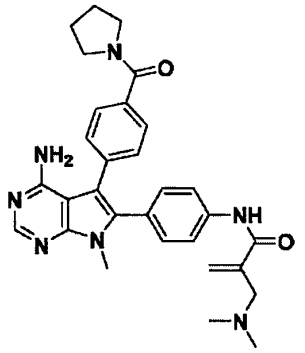
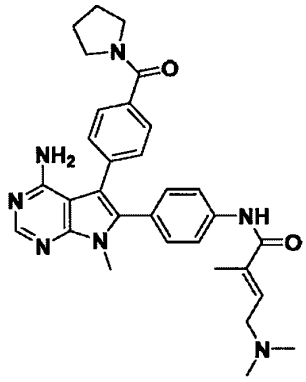
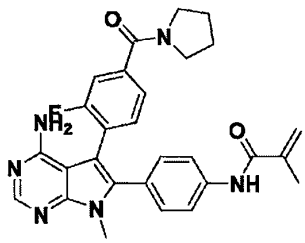
[1014]

化合物	结构	质子 NMR	MS [M+1]
N-(6-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 9.02 - 8.97 (m, 1H), 8.22 (s, 1H), 8.00 (dd, J = 8.6, 2.6 Hz, 1H), 7.74 (dd, J = 8.2, 7.4 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.17 - 7.06 (m, 3H), 7.02 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 5.86 (t, J = 1.0 Hz, 1H), 5.59 (t, J = 1.6 Hz, 1H), 3.77 (s, 3H), 2.36 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	492.20
1-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-1H-吡咯-2(5H)-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.0 Hz, 3H), 7.35 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 6.25 (dt, J = 6.1, 1.9 Hz, 1H), 5.92 (s, 2H), 4.61 (d, J = 2.0 Hz, 2H), 3.62 (s, 3H), 3.44 (dt, J = 13.7, 6.5 Hz, 4H), 1.85 (dt, J = 11.2, 6.2 Hz, 3H), 1.79 (d, J = 6.8 Hz, 1H).	479.20
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)环戊-1-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.20 (s, 1H), 7.73 - 7.67 (m, 2H), 7.52 - 7.45 (m, 2H), 7.26 (dd, J = 8.5, 3.0 Hz, 4H), 6.70 (p, J = 2.2 Hz, 1H), 5.93 (s, 2H), 3.61 (s, 3H), 3.43 (dt, J = 16.5, 6.4 Hz, 4H), 2.57 (tt, J = 6.9, 2.2 Hz, 2H), 2.51 (tt, J = 6.9, 2.2 Hz, 2H), 1.97 - 1.76 (m, 6H).	507.40
5-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 5.1 Hz, 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.62 (dd, J = 5.1, 1.7 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.73 (s, 3H), 3.47 (t, J = 6.8 Hz, 2H), 3.41 (t, J = 6.3 Hz, 2H), 1.84 (dt, J = 19.3, 6.8 Hz, 4H).	424.30

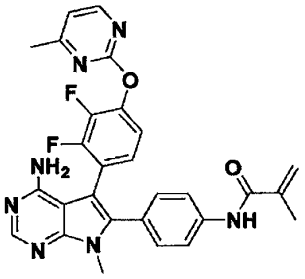
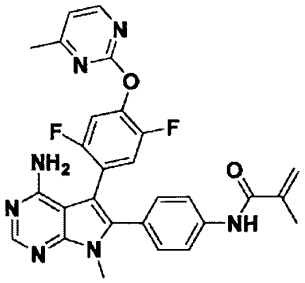
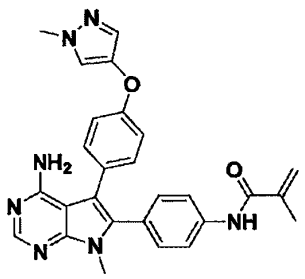
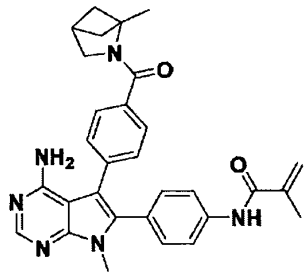
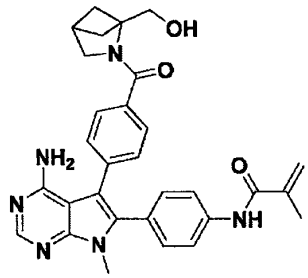
[1015]

化合物	结构	质子 NMR	MS [M+1]
(4-(4-氨基-6-(4-(1,1-二氧离子基异噻唑-2(3H)-基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.39 (dd, J = 13.6, 8.3 Hz, 4H), 7.28 (t, J = 7.0 Hz, 4H), 5.96 (s, 1H), 4.62 (s, 2H), 3.61 (s, 3H), 3.43 (dt, J = 13.0, 6.5 Hz, 4H), 1.84 (dt, J = 18.6, 6.9 Hz, 4H).	515.35
(4-(4-氨基-6-(4-(1,1-二氧离子基-3,4-二氢-2H-1,2-噻嗪-2-基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.41 - 7.18 (m, 6H), 5.93 (dd, J = 80.2, 10.4 Hz, 4H), 4.52 - 4.21 (m, 2H), 3.86 (d, J = 4.3 Hz, 2H), 3.62 (s, 3H), 3.43 (dt, J = 20.3, 6.5 Hz, 4H), 1.84 (dt, J = 18.5, 6.7 Hz, 4H).	529.25
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)环丁-1-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.21 (s, 1H), 7.74 - 7.67 (m, 2H), 7.52 - 7.45 (m, 2H), 7.31 - 7.21 (m, 4H), 6.80 (d, J = 1.3 Hz, 1H), 5.93 (s, 2H), 3.62 (s, 3H), 3.44 (dt, J = 18.5, 6.5 Hz, 4H), 2.74 - 2.68 (m, 2H), 2.46 - 2.40 (m, 2H), 1.83 (dq, J = 18.0, 6.9 Hz, 4H).	493.20
1-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-5,6-二氢吡啶-2(1H)-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.55 - 7.45 (m, 2H), 7.42 - 7.25 (m, 6H), 6.83 (dt, J = 9.7, 4.2 Hz, 1H), 5.91 (dt, J = 9.7, 1.8 Hz, 3H), 3.83 (t, J = 6.9 Hz, 2H), 3.63 (s, 3H), 3.44 (dt, J = 13.7, 6.5 Hz, 4H), 2.48 (d, J = 10.1 Hz, 1H), 1.84 (dq, J = 18.2, 6.8 Hz, 4H).	493.30
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-亚环丁基乙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.66 - 7.56 (m, 2H), 7.54 - 7.42 (m, 2H), 7.32 - 7.15 (m, 4H), 5.81 (t, J = 2.3 Hz, 1H), 3.61 (s, 3H), 3.47 - 3.32 (m, 4H), 3.10 (t, J = 8.2 Hz, 2H), 2.83 (t, J = 7.9 Hz, 2H), 2.05 (p, J = 7.9 Hz, 2H), 1.92 - 1.75 (m, 4H).	507.30

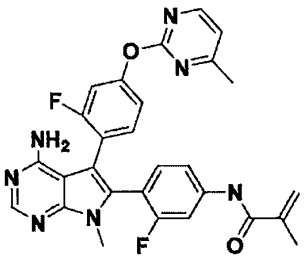
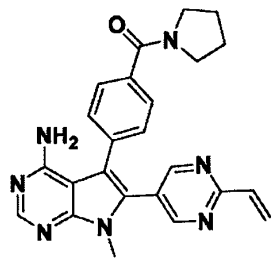
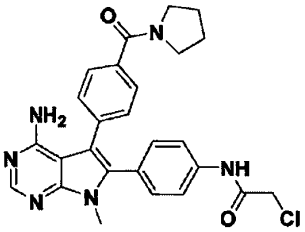
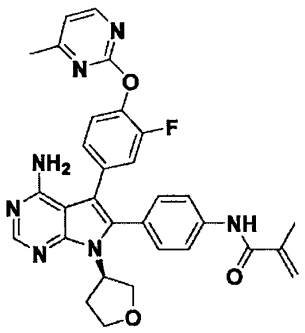
[1016]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-亚环戊基乙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.20 (s, 1H), 7.67 - 7.60 (m, 2H), 7.52 - 7.45 (m, 2H), 7.29 - 7.20 (m, 4H), 6.01 (q, J = 2.4 Hz, 1H), 5.93 (s, 2H), 3.61 (s, 3H), 3.43 (dt, J = 15.8, 6.4 Hz, 4H), 2.75 (t, J = 7.2 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 1.84 (dp, J = 17.8, 6.6 Hz, 4H), 1.64 (dp, J = 34.2, 7.0 Hz, 4H).	521.40
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-((二甲基氨基)甲基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.21 (s, 1H), 7.71 - 7.59 (m, 2H), 7.54 - 7.44 (m, 2H), 7.28 (t, J = 8.0 Hz, 4H), 6.02 (s, 2H), 5.59 (s, 1H), 3.62 (s, 3H), 3.62 - 3.41 (m, 4H), 3.23 (s, 2H), 2.25 (s, 6H), 1.89 - 1.80 (m, 4H).	524.35
(E)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-(二甲基氨基)-2-甲基丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.81 (s, 1H), 8.20 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.28 - 7.05 (m, 4H), 6.89 (t, J = 1.6Hz, 1H), 6. 03 - 5.80 (m 1H), 3.60 (s, 3H),3.47 - 3.41 (m, 4H), 3.04 (d, J = 6.0 Hz, 2H), 2.20 (s, 6H), 1.87 (s, 3H), 1.85 - 1.72 (m, 4H).	538.30
N-(4-(4-氨基-5-(2-氟-4-(吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.20 (s, 1H), 7.71 - 7.64 (m, 2H), 7.36 - 7.30 (m, 3H), 7.27 - 7.21 (m, 2H), 5.92 (s, 2H), 5.80 (d, J = 1.4 Hz, 1H), 5.53 (t, J = 1.4 Hz, 1H), 3.65 (s, 3H), 3.45 (q, J = 7.2 Hz, 4H), 1.95 (t, J = 1.2 Hz, 3H), 1.92 - 1.77 (m, 4H).	499.25

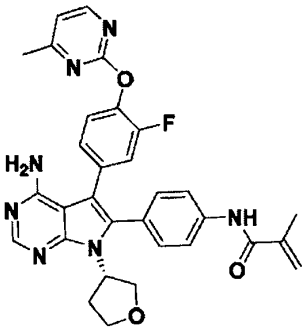
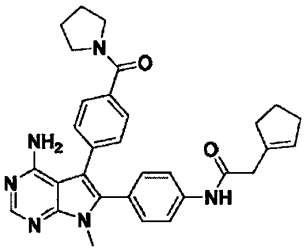
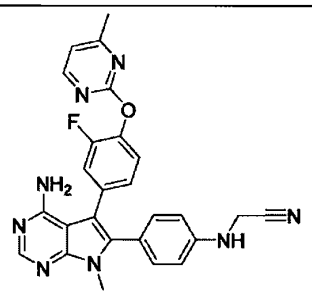
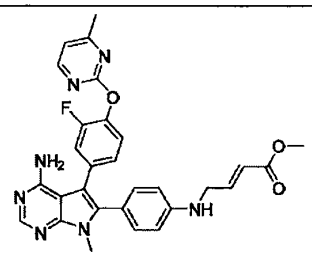
[1017]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(2,3-二氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.42 - 6.94 (m, 5H), 6.04 (s, 2H), 5.80 (s, 1H), 5.54 (s, 1H), 3.64 (s, 3H), 2.43 (s, 3H), 1.95 (s, 3H).	528.30
N-(4-(4-氨基-5-(2,5-二氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.81 - 7.71 (m, 2H), 7.43 - 7.27 (m, 4H), 7.22 (d, J = 5.1 Hz, 1H), 6.00 (s, 2H), 5.85 - 5.77 (m, 1H), 5.54 (t, J = 1.5 Hz, 1H), 3.63 (s, 3H), 2.43 (s, 3H), 1.96 (t, J = 1.3 Hz, 3H).	528.30
N-(4-(4-氨基-7-甲基-5-(4-((1-甲基-1H-吡唑-4-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.18 (s, 1H), 7.77 (s, 1H), 7.74 - 7.67 (m, 2H), 7.39 (s, 1H), 7.30 - 7.23 (m, 2H), 7.23 - 7.15 (m, 2H), 7.00 - 6.92 (m, 2H), 5.80 (s, 2H), 5.54 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.59 (s, 3H),, 1.95 (d, J = 1.5 Hz, 3H).	480.35
N-(4-(4-氨基-7-甲基-5-(4-(1-甲基-2-氮杂-双环[2.1.1]己烷-2-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.21 (s, 1H), 7.73 - 7.67 (m, 2H), 7.50 (d, J = 7.7 Hz, 2H), 7.29 - 7.22 (m, 4H), 5.80 (s, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.62 (s, 3H), 3.40 (s, 2H), 2.71 (d, J = 3.1 Hz, 1H), 1.95 (d, J = 1.4 Hz, 3H), 1.76 (d, J = 4.8 Hz, 2H), 1.60 (s, 3H), 1.50 (dd, J = 4.5, 1.9 Hz, 2H).	507.3
N-(4-(4-氨基-5-(4-(1-(羟基甲基)-2-氮杂-双环[2.1.1]己烷-2-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 7.9 Hz, 2H), 7.27 (dd, J = 8.4, 3.0 Hz, 4H), 5.80 (s, 1H), 5.53 (s, 1H), 5.12 (t, J = 6.5 Hz, 1H), 3.93 (d, J = 6.4 Hz, 2H), 3.62 (s, 3H), 3.46 (s, 2H), 2.74 (d, J = 3.2 Hz, 1H), 1.95 (s, 3H), 1.93 - 1.87 (m, 2H), 1.47 (dd, J = 4.6, 1.8 Hz, 2H).	523.2

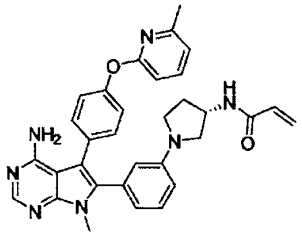
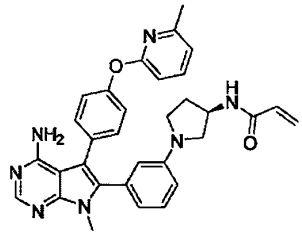
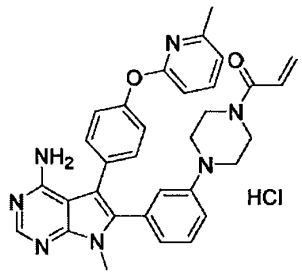
[1018]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(2-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.77 (dd, J = 12.5, 2.0 Hz, 1H), 7.50 (dd, J = 8.5, 2.0 Hz, 1H), 7.26 (t, J = 8.4 Hz, 2H), 7.18 (d, J = 5.0 Hz, 2H), 7.07 (d, J = 8.3 Hz, 1H), 5.82 (s, 1H), 5.58 (s, 1H), 3.57 (s, 3H), 2.42 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H).	528.40
(4-(4-氨基-7-甲基-6-(2-乙烯基嘧啶-5-基)-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 2H), 8.25 (s, 1H), 7.54 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 6.84 (dd, J = 17.3, 10.5 Hz, 1H), 6.57 (dd, J = 17.3, 2.0 Hz, 1H), 5.81 (dd, J = 10.5, 2.0 Hz, 1H), 3.72 (s, 3H), 3.45 (dt, J = 16.8, 6.5 Hz, 4H), 1.84 (dq, J = 18.7, 6.8 Hz, 4H).	462.35
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-氯乙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.21 (s, 1H), 7.68 (s, 3H), 7.61 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 7.7 Hz, 2H), 7.28 (dd, J = 15.1, 7.9 Hz, 4H), 5.94 (s, 2H), 4.27 (s, 2H), 3.61 (s, 3H), 3.45 (dd, J = 16.0, 8.9 Hz, 4H), 1.84 (dd, J = 18.3, 6.3 Hz, 5H).	489.35
(R)-N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-(四氢呋喃-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.81 - 7.74 (m, 2H), 7.37 - 7.28 (m, 3H), 7.24 - 7.15 (m, 2H), 7.11 (dd, J = 8.2, 2.0 Hz, 1H), 5.95 (s, 1H), 5.80 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 4.68 (p, J = 8.2 Hz, 1H), 4.18 (dt, J = 15.3, 8.2 Hz, 2H), 3.96 (t, J = 8.2 Hz, 1H), 3.83 (q, J = 7.5 Hz, 1H), 2.77 (dq, J = 14.1, 7.2 Hz, 1H), 2.41 (s, 3H), 2.17 (dd, J = 10.1, 4.9 Hz, 1H), 1.96 (t, J = 1.2 Hz, 3H).	566.25

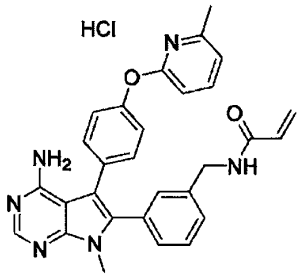
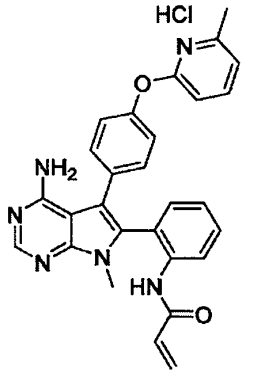
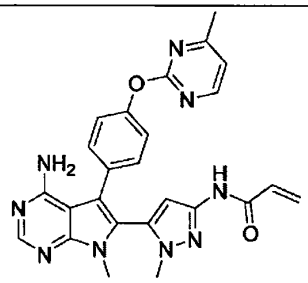
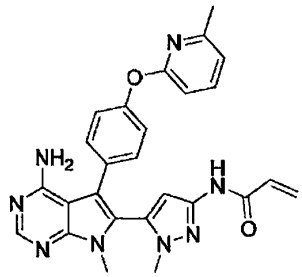
[1019]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-(四氢呋喃-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.81 - 7.74 (m, 2H), 7.37 - 7.28 (m, 3H), 7.25 - 7.15 (m, 2H), 7.14 - 7.07 (m, 1H), 6.12 (s, 1H), 5.80 (s, 1H), 5.55 (d, J = 1.9 Hz, 1H), 4.68 (q, J = 8.3 Hz, 1H), 4.24 - 4.12 (m, 2H), 3.97 (t, J = 8.2 Hz, 1H), 3.83 (q, J = 7.4 Hz, 1H), 2.76 (dq, J = 14.2, 7.3 Hz, 1H), 2.41 (s, 3H), 2.19 (s, 1H), 1.96 (t, J = 1.2 Hz, 3H).	566.20
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-(环戊-1-烯-1-基)乙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.20 (s, 1H), 7.64 - 7.57 (m, 2H), 7.52 - 7.45 (m, 2H), 7.29 - 7.21 (m, 4H), 5.92 (s, 2H), 5.52 (s, 1H), 3.60 (s, 3H), 3.43 (dt, J = 18.2, 6.4 Hz, 4H), 3.13 (s, 2H), 2.30 (t, J = 7.6 Hz, 4H), 1.84 (tdd, J = 12.4, 7.0, 3.8 Hz, 6H).	521.35
2-((4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)氨基)乙腈		^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41-8.36 (m, 2H), 8.21 (s, 1H), 7.48 (s, 1H), 7.41-7.38 (m, 2H), 7.31-7.28 (m, 2H), 6.96 (s, 1H), 5.14 (s, 2H), 4.28 (m, 2H), 3.21 (s, 1H), 2.85-2.81 (m, 2H), 2.54 (s, 3H), 2.40-2.36 (m, 2H)	460.3
(2*E*)-4-{[4-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]氨基}丁-2-烯甲酯		^{1}H NMR (400 MHz, CD_3OD): δ 8.42 (d, J = 5.2 Hz, 1H), 8.19 (s, 1H), 7.29-7.25 (m, 1H), 7.18-7.02 (m, 6H), 6.65 (d, J = 8.4 Hz, 2H), 6.03(d, J = 15.6 Hz, 1H), 3.99-3.97 (m, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 2.51 (s, 3H).	540.3

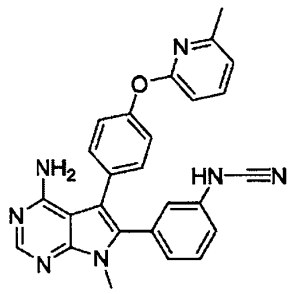
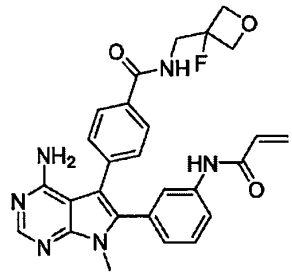
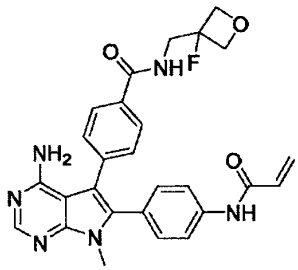
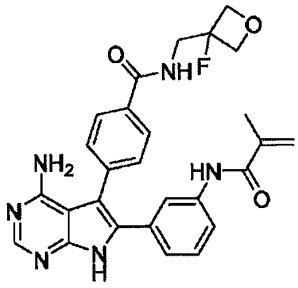
[1020]

化合物	结构	质子 NMR	MS [M+1]
N-[(3*S*)-1--[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]吡咯烷-3-基]丙-2-烯酰胺		^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1 H), 7.62 - 7.54 (m, 1H), 7.33 - 7.26 (m, 2H), 7.08 - 7.04 (m, 2H), 6.93 - 6.88 (m, 2H), 6.70 - 6.62 (m, 2H), 6.59 - 6.52 (m, 1H), 6.38 - 6.25 (m, 2H), 6.10 - 5.99 (m, 1H), 5.93 - 5.83 (m, 1H) , 5.05 - 4.96 (m, 2H), 4.76 - 4.63 (m, 1H), 3.75 (s, 3H) 3.53 - 3.45 (m, 1H), 3.39 - 3.05 (m, 3H), 2.45 (s, 3H), 2.36 - 2.26 (m, 1H), 2.06 - 1.96 (m, 1H).	546.1
N-[(3*R*)-1-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]吡咯烷-3-基]丙-2-烯酰胺		^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1 H), 7.62 - 7.54 (m, 1H), 7.33 - 7.26 (m, 2H), 7.08 - 7.04 (m, 2H), 6.93 - 6.88 (m, 2H), 6.70 - 6.62 (m, 2H), 6.59 - 6.52 (m, 1H), 6.38 - 6.25 (m, 2H), 6.10 - 5.99 (m, 1H), 5.93 - 5.83 (m, 1H) , 5.05 - 4.96 (m, 2H), 4.76 - 4.63 (m, 1H), 3.75 (s, 3H) 3.53 - 3.45 (m, 1H), 3.39 - 3.05 (m, 3H), 2.45 (s, 3H), 2.36 - 2.26 (m, 1H), 2.06 - 1.96 (m, 1H)	546.1
1-{4-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]哌嗪-1-基}丙-2-烯-1-酮盐酸盐		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.73-7.70 (m, 1H), 7.63-7.60 (d, J = 8.0 Hz, 1H), 7.49-7.45 (m, 2H), 7.35-7.28 (m, 3H), 7.32-7.28 (m, 3H), 7.14-7.10 (m, 2H), 7.02-7.00 (d, J = 7.6 Hz, 1H), 6.79-6.76 (m, 1H), 6.69-6.59 (m, 1H), 6.49 (s, 1H), 6.23-6.15 (m, 1H), 5.75-5.70 (m, 1H), 4.69 (s, 1H), 4.55-4.47 (d, J = 32.4 Hz, 2H), 4.32 (s, 1H), 3.75-3.73 (d, J = 6.8 Hz, 3H), 2.31-2.29 (d, J = 7.2 Hz, 3H).	529.3

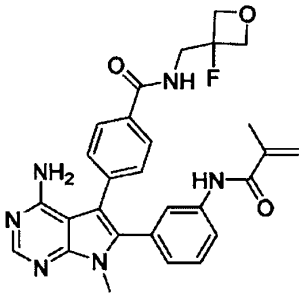
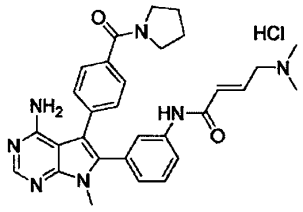
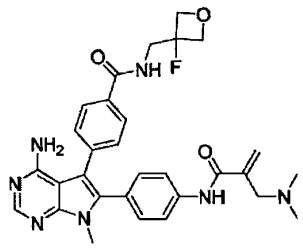
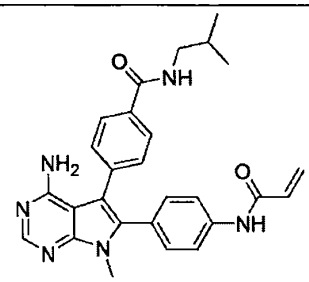
[1021]

化合物	结构	质子 NMR	MS [M+1]
N-{[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]甲基}丙-2-烯酰胺盐酸盐		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71-8.67 (m, 1H), 8.58 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.44 - 7.20 (m, 6H), 7.15 - 7.00 (m, 3H), 6.81 (d, J = 8.0 Hz, 1H), 6.32 - 6.23 (m, 1H), 6.16 - 6.05 (m, 1H), 5.61 (dd, J = 2.1, 10.0 Hz, 1H), 4.36 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H), 2.37 (s, 3H).	491.1
N-[2-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]丙-2-烯酰胺盐酸盐		^{1}H NMR (400 MHz, CD_3OD): δ 8.10 (s, 1H), 7.66 - 7.55 (m, 2H), 7.40 - 7.32 (m, 2H), 7.28 - 7.19 (m, 1H), 7.11 (br d, J = 7.8 Hz, 2H), 6.90 (t, J = 7.2 Hz, 3H), 6.63 (d, J = 8.4 Hz, 1H), 6.17 - 5.99 (m, 2H), 5.58 - 5.50 (m, 1H), 5.10 (s, 1H), 4.88 - 4.82 (m, 4H), 4.51 (s, 11H), 3.54 (s, 4H), 2.36 - 2.27 (m, 3H)	477.2
N-[5-(4-氨基-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7*H* 吡咯并[2,3-*d*]嘧啶-6-基)-1-甲基-1*H*-吡唑-3-基]丙-2-烯酰胺		^{1}HNMR (400 MHz, 甲醇-d_4): δ 8.30 (d, J = 5.0 Hz, 1H), 8.14 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 5.0 Hz, 1H), 6.82 (s, 1H), 6.40 - 6.23 (m, 2H), 5.68 (dd, J = 2.4, 9.8 Hz, 1H), 4.50 (s, 4H), 3.61 - 3.56 (m, 3H), 2.38 (s, 3H).	482.3
N-[5-(4-氨基 7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)-1-甲基-1*H*-吡唑-3-基]丙-2-烯酰胺		^{1}HNMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.28 (s, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.54 - 7.45 (m, 3H), 7.35 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.00 - 6.94 (m, 1H), 6.93 - 6.87 (m, 1H), 6.58 (d, J = 2.4 Hz, 1H), 4.01 (s, 3H), 3.88 - 3.75 (m, 4H), 2.45 (s, 3H).	481.3

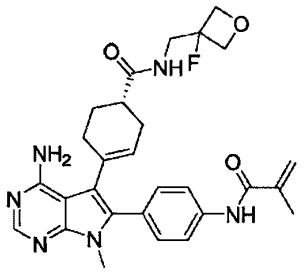
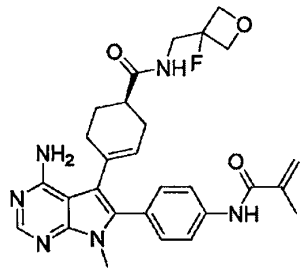
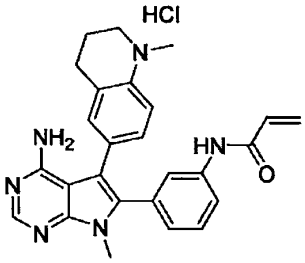
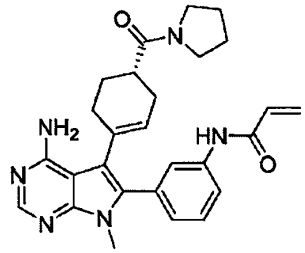
[1022]

化合物	结构	质子 NMR	MS [M+1]
[3-[4-氨基-7-甲基-5-[4-[(6-甲基-2-吡啶基)氧基]苯基]吡咯并[2,3-*d*]嘧啶-6-基]苯基]氰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.2 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 7.6 Hz, 2H), 7.04-7.00 (m, 2H), 6.98-6.93 (m, 1H), 6.81 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.93 (br, 1H), 3.60 (s, 3H), 2.35 (s, 3H).	448.2
4-{4-氨基-7-甲基-6-[3-(丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}-N-[(3-氟氧杂环丁-3-基)甲基]苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.83-8.77 (m, 1H), 8.22 (s, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.73-7.64 (m, 2H), 7.38-7.29 (m, 3H), 6.99 (d, J = 7.6 Hz, 1H), 6.47-6.35 (m, 1H), 6.30-6.21 (m, 1H), 5.98 (s, 1H), 5.79-5.73 (m, 1H), 4.73-4.55(m, 4H), 3.82 (d, J = 6.0 Hz, 1H), 3.76 (d, J = 6.0 Hz 1H), 3.60 (s, 3H).	501.1
4-{4-氨基-7-甲基-6-[4-(丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}-N-[(3-氟氧杂环丁-3-基)甲基]苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.82-8.74 (m, 1H),8.20 (s, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.33-7.24 (m, 4H), 6.48-6.38 (m, 1H), 6.30-6.23 (m, 1H), 5.93 (br, 1H), 5.80-5.74 (m, 1H), 4.71-4.52 (m, 4H), 3.83-3.73 (m, 2H), 3.60 (s, 3H).	501.1
4-[4-氨基-6-[3-(2-甲基丙-2-烯酰基氨基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基]-N-[(3-氟氧杂环丁-3-基)甲基]苯甲酰胺		^{1}HNMR (400 MHz, DMSO-d_6): δ 12.16 (br, 1H), 9.81 (s, 1H), 8.86 (t, J = 6.0 Hz, 1H), 8.14 (s, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.81 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.21 (m, 1H), 6.89 (d, J = 8.0 Hz, 1H), 5.75 (s, 1H), 5.51(s, 1H), 4.74-4.59 (m, 4H), 3.82 (dd, J = 19.6 Hz, 6.6 Hz, 2H), 1.92 (s, 3H).	501.1

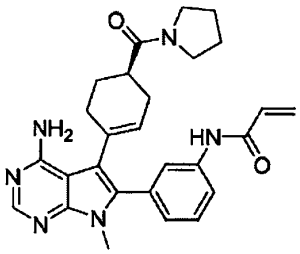
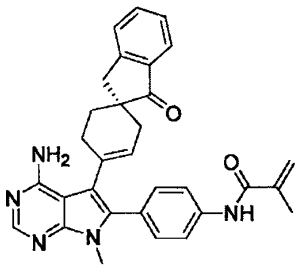
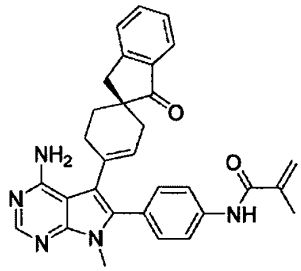
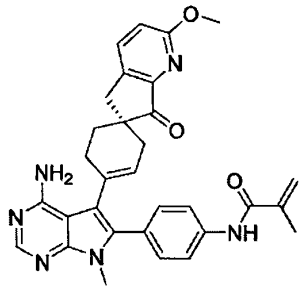
[1023]

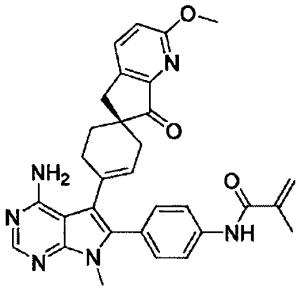
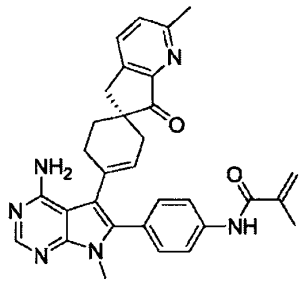
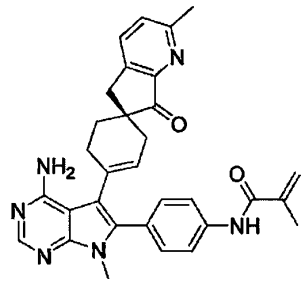
化合物	结构	质子 NMR	MS [M+1]
4-{4-氨基-7-甲基-6-[3-(2-甲基丙-2-烯酰胺基)苯基]-7*H*-吡咯并[2,3-*d*]嘧啶-5-基}-*N*-[(3-氟氧杂环丁-3-基)甲基]苯甲酰胺		^{1}HNMR (400 MHz, DMSO-d_6): δ 9.88 (s, 1H), 8.81-8.78 (m, 1H), 8.22 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.34-7.29 (m, 3H), 6.95 (d, J = 7.6 Hz, 1H), 5.78 (s, 1H), 5.52 (s, 1H), 4.70-4.57 (m, 4H), 3.82-3.75 (m, 2H), 3.60 (s, 3H), 1.93 (s, 3H).	515.1
(2*E*)-*N*-(3-{4-氨基-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7*H*-吡咯并[2,3-*d*]嘧啶-6-基}苯基)-4-(二甲基氨基)丁-2-烯酰胺盐酸盐		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 10.72 (s, 1H), 8.60 (s, 1H), 7.77-7.73 (m, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.43-7.39 (m, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.83-6.76 (m, 1H), 6.50 (d, J = 7.2 Hz, 1H), 3.92-3.89 (m, 2H), 3.71 (s, 3H), 3.45-3.40 (m, 4H), 2.74 (d, J = 4.0 Hz, 6H), 1.88-1.76 (m, 4H).	524.4
4-[4-氨基-6-(4-{2-[(二甲基氨基)甲基]丙-2-烯酰胺基}苯基)-7-甲基-7*H*-吡咯并[2,3-d]嘧啶-5-基]-*N*-[(3-氟氧杂环丁-3-基)甲基]苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83-8.74 (m, 1H), 8.16 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 8.0 Hz, 2H), 6.30-6.20 (m, 1H), 5.83 (br, 1H), 5.36 (s, 1H), 5.12 (s, 1H), 4.74-4.53 (m, 4H), 3.89-3.70 (m, 4H), 3.57 (s, 3H), 2.91-2.78 (d, J = 16.0 Hz, 6H).	558.2
4-{4-氨基-7-甲基-6-[4-(丙-2-烯酰胺基)苯基]-7*H*-吡咯并[2,3-*d*]嘧啶-5-基}-*N*-(2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.47-6.34 (m, 2H), 5.81-5.78 (m, 2H), 3.8 (s, 3H), 3.19 (d, J = 6.8 Hz, 1H), 1.95-1.88 (m, 1H), 0.95 (d, J = 6.4 Hz, 6H).	469.2

[1024]

化合物	结构	质子 NMR	MS [M+1]
(1*S*)-4-{4-氨基-7-甲基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}-N-[(3-氟氧杂环丁-3-基)甲基]环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 1H), 8.35-8.24 (m, 1H), 8.10 (s, 1H), 7.81 (d, J = 12.0 Hz, 2H), 7.43 (d, J = 12.0 Hz, 2H), 6.60 - 6.24 (m, 2H), 5.92 - 5.72 (m, 2H), 5.55 (s, 1H), 4.68 - 4.43 (m, 4H), 3.63 - 3.53 (m, 4H), 2.59 - 2.53 (m, 1H), 2.38 - 2.16 (m, 2H), 1.97 (s, 3H), 1.91-1.84 (m, 2H), 1.75-1.60 (m, 2H).	519.1
(1*R*)-4-{4-氨基-7-甲基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}-N-[(3-氟氧杂环丁-3-基)甲基]环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 8.26 (t, J = 6.0 Hz, 1H), 8.10 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.44 (br s, 2H), 5.88 - 5.70 (m, 2H), 5.55 (s, 1H), 4.64 - 4.46 (m, 4H), 3.62 - 3.53 (m, 4H), 2.59 - 2.54 (m, 1H), 2.39 - 2.16 (m, 2H), 1.97 (s, 3H), 1.93-83 (m, 2H), 1.72-1.60 (m, 2H).	519.1
N-{3-[4-氨基-7-甲基-5-(1-甲基-1,2,3,4-四氢喹啉-6-基)-7*H*-吡咯并[2,3-d]嘧啶-6-基]苯基}丙-2-烯酰胺盐酸盐		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.60 - 10.32 (m, 1H), 8.59 - 8.40 (m, 1H), 7.78 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.42 - 7.33 (m, 1H), 7.06 - 7.00 (m, 1H), 6.93 - 6.84 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.52 - 6.41 (m, 1H), 6.25 (dd, J = 1.6, 16.8 Hz, 1H), 5.80 - 5.71 (m, 1H), 3.65 - 3.64 (m, 3H), 3.27 - 3.16 (m, 2H), 2.83 (s, 3H), 2.68 - 2.59 (m, 2H), 1.86 (m, 2H)	439.1
N-(3-{4-氨基-7-甲基-5-[(4S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7*H*-吡咯并[2,3-d]嘧啶-6-基}苯基)丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.11 (s, 1H), 7.90 (s, 1H), 7.66 (dd, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.530 (br, 2H), 6.491-6.423 (m, 1H), 6.35 - 6.21 (m, 1H), 5.83 - 5.71 (m, 2H), 3.69 - 3.53 (m, 3H), 3.52 - 3.40 (m, 2H), 3.42 - 3.40 (m, 1H), 3.29 - 3.20 (m, 2H), 2.81 (m, 1H), 2.37 - 2.13 (m, 2H), 1.98 - 1.58 (m, 8H).	471.1

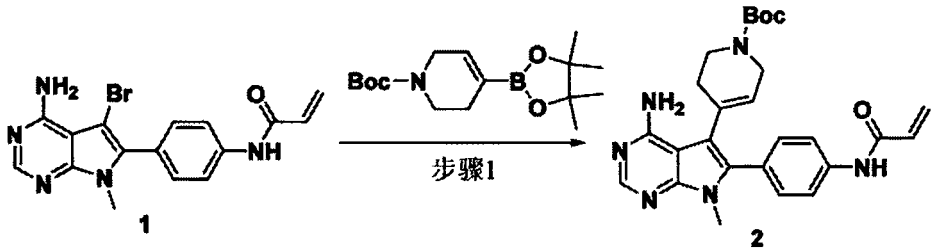
[1025]

化合物	结构	质子 NMR	MS [M+1]
N-(3-{4-氨基-7-甲基-5-[(4*R*)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7*H*-吡咯并[2,3-d]嘧啶-6-基}苯基)丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H), 8.11 (s, 1H), 7.90 (s, 1H), 7.67 (dd, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.526 (br, 2H), 6.493-6.425(m, 1H), 6.33 - 6.22 (m, 1H), 5.85 - 5.69 (m, 2H), 3.60 (s, 3H), 3.52 - 3.40 (m, 4H), 3.34 - 3.20 (m, 3H), 2.88 - 2.74 (m, 1H), 2.38 - 2.14 (m, 2H), 2.01 - 1.56 (m, 8H).	471.1
N-(4-{4-氨基-7-甲基-5-[(1*R*)-3'-侧氧基-1',3'-二氢螺[环己烷-1,2'-茚]-3-烯-4-基]-7*H*-吡咯并[2,3-*d*]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		^{1}H NMR (400MHz, 甲醇-d_4) δ 8.16 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.75 - 7.64 (m, 2H), 7.58 - 7.48 (m, 3H), 7.47 - 7.39 (m, 1H), 5.98 (s, 1H), 5.87 (s, 1H), 5.58 (d, J = 0.8 Hz, 1H), 3.68 (s, 3H), 3.01 (s, 2H), 2.70 - 2.43 (m, 1H), 2.37 - 2.17 (m, 2H), 2.09 (s, 3H), 2.06 - 1.96 (m, 1H), 1.86-1.78 (m, 1H), 1.69 - 1.56 (m, 1H).	504.1
N-(4-{4-氨基-7-甲基-5-[(1*S*)-3'-侧氧基-1',3'-二氢螺[环己烷-1,2'-茚]-3-烯-4-基]-7*H*-吡咯并[2,3-*d*]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		^{1}HNMR (400MHz, 甲醇-d_4) δ 8.06 (s, 1H), 7.79 - 7.66 (m, 2H), 7.64 - 7.50 (m, 2H), 7.46 - 7.36 (m, 3H), 7.35 - 7.28 (m, 1H), 5.87 (s, 1H), 5.75 (s, 1H), 5.46 (d, J = 0.8 Hz, 1H), 3.58 (s, 3H), 2.89 (s, 2H), 2.55 - 2.34 (m, 1H), 2.27 - 2.04 (m, 2H), 1.97 (s, 3H), 1.94 - 1.87 (m, 1H), 1.72-1.66 (m, 1H), 1.58 - 1.47 (m, 1H).	504.1
N-(4-{4-氨基-5-[(1*R*)-2'-甲氧基-7'-侧氧基-5',7'-二氢螺[环己烷-1,6'-环戊并[*b*]吡啶]-3-烯-4-基]-7-甲基-7*H*-吡咯并[2,3-*d*]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		^{1}H NMR (400MHz, DMSO-d_6): δ 9.97 (s, 1H), 8.13 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 1H), 6.51 (br, 2H), 5.87-5.78 (m, 2H), 5.56 (s, 1H), 3.88 (s, 3H), 3.60 (s, 3H), 2.89-2.74 (m, 2H), 2.47-2.42 (m, 2H), 2.14-2.09 (m, 2H), 2.05-1.98 (m, 4H), 1.83 - 1.66 (m, 1H), 1.58 - 1.45 (m, 1H).	535.1

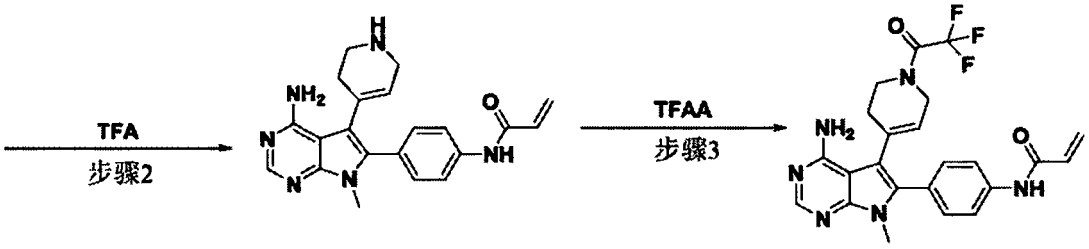
化合物	结构	质子 NMR	MS [M+1]
N-(4-{4-氨基-5-[(1*S*)-2'-甲氧基-7'-侧氧基-5',7'-二氢螺[环己烷-1,6'-环戊并[b]吡啶]-3-烯-4-基]-7-甲基-7*H*-吡咯并[2,3-*d*]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		^{1}H NMR (400MHz, DMSO-d_6): δ 9.99 (s, 1H), 8.13 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 6.53 (br, 2H), 5.90 - 5.80 (m, 2H), 5.56 (s, 1H), 3.89 (s, 3H), 3.61 (s, 3H), 2.92-2.77 (m, 2H), 2.47-2.43 (m, 1H), 2.14-2.10 (m, 2H), 2.02-1.99 (m, 4H), 1.81-1.69 (m, 1H), 1.57-1.46 (m, 1H).	535.1
N-(4-{4-氨基-7-甲基-5-[(1*R*)-2'-甲基-7'-侧氧基-5',7'-二氢螺[环己烷-1,6'-环戊并[*b*]吡啶]-3-烯-4-基]-7*H*-吡咯并[2,3-*d*]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		^{1}H NMR (400MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.79 - 7.67 (m, 3H), 7.61 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 5.96 (br, 1H), 5.86 (s, 1H), 5.54 (s, 1H), 3.70 (s, 3H), 2.93 (s, 2H), 2.68 (s, 3H), 2.61-2.56 (m, 1H), 2.45 - 2.15 (m, 3H), 2.12 (s, 3H), 2.05 - 1.92 (m, 1H), 1.89 - 1.78 (m, 1H)	519.1
N-(4-{4-氨基-7-甲基-5-[(1*S*)-2'-甲基-7'-侧氧基-5',7'-二氢螺[环己烷-1,6'-环戊并[*b*]吡啶]-3-烯-4-基]-7*H*-吡咯并[2,3-*d*]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		^{1}H NMR (400MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.79 - 7.69 (m, 3H), 7.65 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 5.96 (s, 1H), 5.86 (s, 1H), 5.54 (s, 1H), 3.72 (s, 3H), 2.94 (s, 2H), 2.68 (s, 3H), 2.59-2.53 (m, 1H), 2.43 - 2.26 (m, 3H), 2.12 (s, 3H), 2.02-1.92 (m, 1H), 1.82-1.71 (m, 1H).	519.1

[1026]

[1027] 流程2



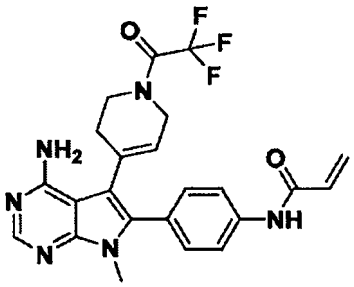
[1028]



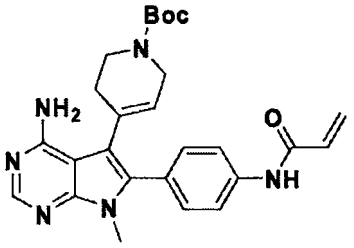
[1029] 实例4

[1030] N-(4-(4-氨基-7-甲基-5-(1-(2,2,2-三氟乙酰基)-1,2,3,6-四氢吡啶-4-基)-

7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺

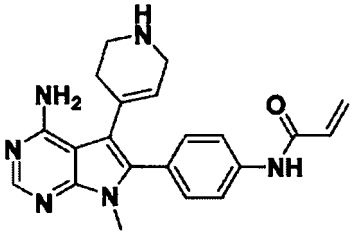
[1031] 

[1032] 4-(6-(4-丙烯酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-3,6-二氢吡啶-1(2H)-甲酸叔丁酯

[1033] 

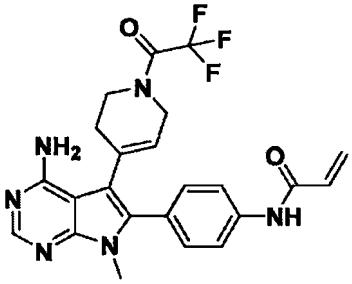
[1034] 步骤1:向圆底烧瓶中装入N-(4-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)丙-2-烯酰胺(200mg,537μmol)、4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,2,3,6-四氢吡啶-1-甲酸叔丁酯(199mg,644μmol)、Pd(dtbpf)Cl_2(34.9mg,53.7μmol)、K_3PO_4(341mg,1.61mmol)、5mL DMF及搅拌棒。在90℃下搅拌溶液2小时。反应混合物用水(50mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(2g柱;用庚烷/乙酸乙酯3:1洗脱)。真空浓缩,产生呈黄色油状的4-{4-氨基-7-甲基-6-[4-(丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}-1,2,3,6-四氢吡啶-1-甲酸叔丁酯(121mg,48%)。

[1035] N-(4-(4-氨基-7-甲基-5-(1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺

[1036] 

[1037] 步骤2:向圆底烧瓶中装入4-{4-氨基-7-甲基-6-[4-(丙-2-烯酰胺基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}-1,2,3,6-四氢吡啶-1-甲酸叔丁酯(30mg,63.2μmol)、0.2mL TFA、0.8mLDCM及搅拌棒。在室温下搅拌溶液1小时。将反应混合物过滤且真空浓缩。所得粗物质通过HPLC纯化(乙腈/水/0.1%甲酸)。冻干产生呈白色无定形固体状的N-{4-[4-氨基-7-甲基-5-(1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}丙-2-烯酰胺(16.8mg,71%)。

[1038] N-(4-(4-氨基-7-甲基-5-(1-(2,2,2-三氟乙酰基)-1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺

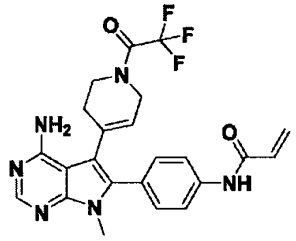
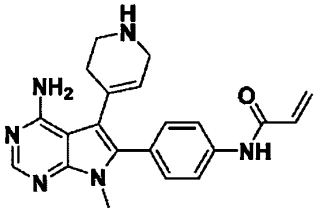
[1039] 

[1040] 步骤3:向圆底烧瓶中装入N-{4-[4-氨基-7-甲基-5-(1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}丙-2-烯酰胺(40mg,106μmol)、TEA(32.1mg,318μmol)、DMAP(1.29mg,10.6μmol)、5mL DCM及搅拌棒。在0℃下逐滴添加TFAA。在室温下搅拌溶液1小时。反应混合物用水(30mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(乙腈/水/0.1%甲酸)。冻干产生呈白色无定形固体状的N-(4-{4-氨基-7-甲基-5-[1-(2,2,2-三氟乙酰基)-1,2,3,6-四氢吡啶-4-基]-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)丙-2-烯酰胺(27.9mg,37%)。

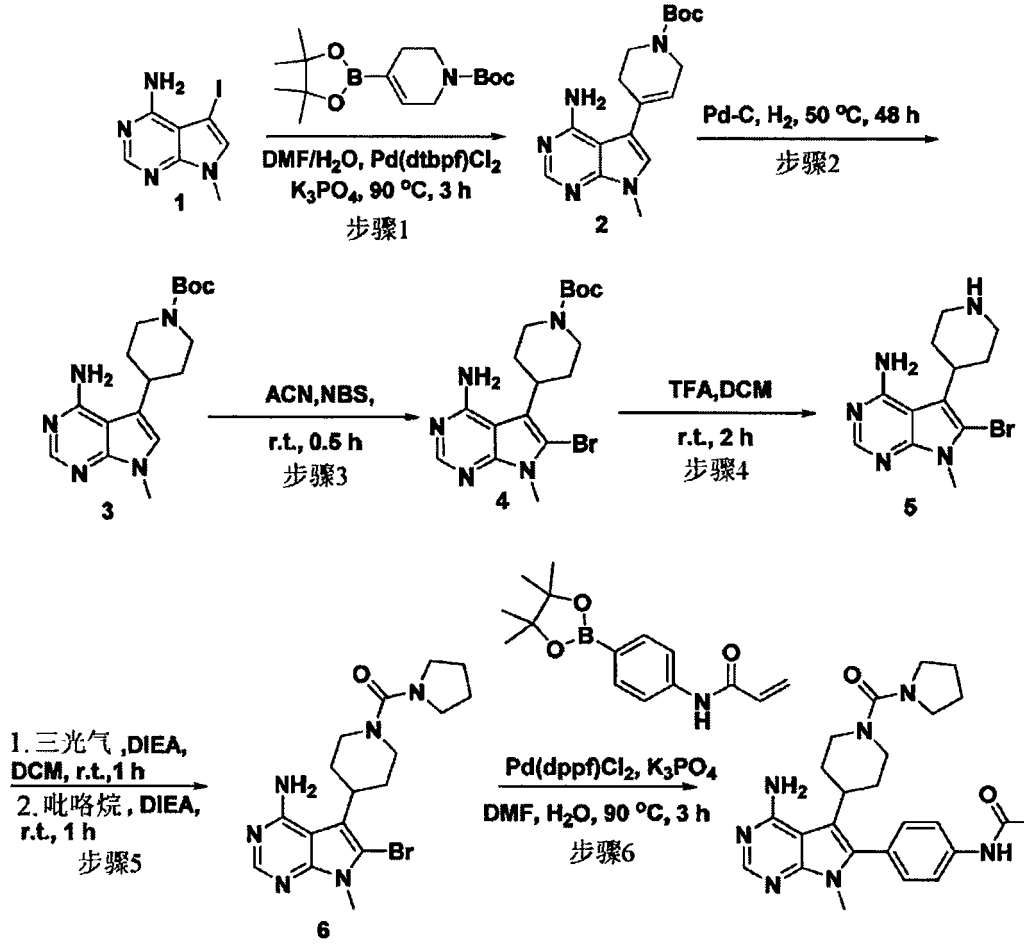
[1041] 根据实例4的方法制备的其它化合物描绘于下表3中。

[1042] 表3.其它示例性化合物

[1043]

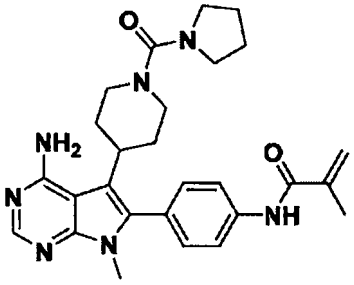
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-(2,2,2-三氟乙酰基)-1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.33 (d, J = 2.8 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.87 - 7.68 (m, 2H), 7.47 - 7.39 (m, 2H), 6.49 - 6.28 (m, 3H), 5.85 - 5.70 (m, 2H), 4.30 - 4.09 (m, 2H), 3.65 - 3.52 (m, 5H), 2.09 (s, 2H).	471.1
N-(4-(4-氨基-7-甲基-5-(1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.30 (d, J = 28.0 Hz, 1H), 8.21 - 8.08 (m, 1H), 7.80 - 7.56 (m, 2H), 7.44-7.39 (m, 2H), 6.56 - 6.05 (m, 2H), 5.80 (d, J = 10.4 Hz, 1H), 3.57-3.46 (m, 4H), 3.16 (d, J = 46.0 Hz, 2H), 2.77 - 2.63 (m, 2H), 2.00 (m, J = 46.4 Hz, 2H).	375.2

[1044] 流程3

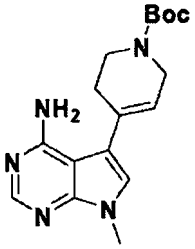
[1045] 

[1046] 实例5

[1047] N-(4-(4-氨基-7-甲基-5-(1-(吡咯烷-1-羰基)哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

[1048] 

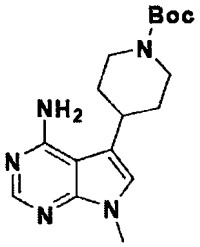
[1049] 4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-3,6-二氢吡啶-1(2H)-甲酸叔丁酯

[1050] 

[1051] 步骤1:向圆底烧瓶中装入5-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(3.00g,10.9mmol)、4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,2,3,6-四氢吡啶-1-

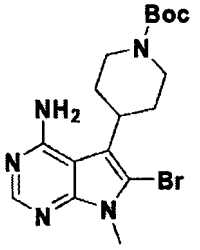
甲酸叔丁酯(4.01g,13.0mmol)、Pd(dtbpf)Cl_2(710mg,1.09mmol)、K_3PO_4(6.91g,32.6mmol)及搅拌棒。添加DMF(45mL)及H_2O(3mL),且在90℃下搅拌溶液3小时。混合物用EtOAc(300mL)稀释且用水(3*100mL)洗涤,浓缩有机相且通过使用DCM:MeOH=25:1的硅胶柱纯化粗产物,得到呈棕色油状的4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}-1,2,3,6-四氢吡啶-1-甲酸叔丁酯(2.97g,83%)。

[1052] 4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯

[1053] 

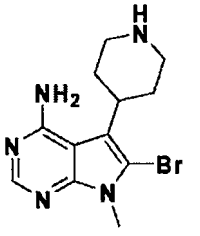
[1054] 步骤2:向圆底烧瓶中装入4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}-1,2,3,6-四氢吡啶-1-甲酸叔丁酯(1.70g,5.16mmol)、Pd/C(326mg,154μmol)及搅拌棒。添加MeOH(50mL),且在50℃下、在H_2下搅拌溶液48小时。过滤混合物且用MeOH洗涤5次,浓缩滤液且获得呈棕色油状的4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}哌啶-1-甲酸叔丁酯(900mg,53%)。

[1055] 4-(4-氨基-6-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯

[1056] 

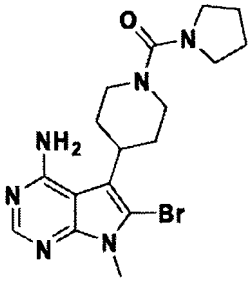
[1057] 步骤3:向圆底烧瓶中装入4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}哌啶-1-甲酸叔丁酯(800mg,2.41mmol)、NBS(428mg,2.41mmol)及搅拌棒。添加ACN(20mL),且在25℃下搅拌溶液0.5小时。在减压下浓缩混合物且获得呈棕色固体状的产物4-{4-氨基-6-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}哌啶-1-甲酸叔丁酯(500mg,51%)。粗产物不经进一步纯化即用于下一步骤中。

[1058] 6-溴-7-甲基-5-(哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1059] 

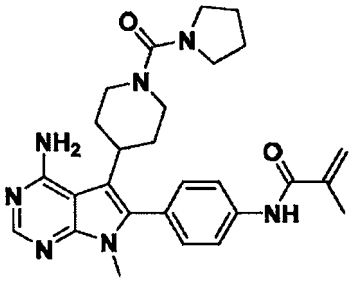
[1060] 步骤4:向圆底烧瓶中装入4-{4-氨基-6-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}哌啶-1-甲酸叔丁酯(500mg,1.21mmol)、DCM(5mL)及搅拌棒。添加TFA(0.5mL),且在25℃下搅拌溶液2小时。在减压下浓缩混合物,且用DCM(30mL)稀释,用$NaHCO_3$饱和水溶液(3*15mL)洗涤,浓缩有机相且获得呈棕色油状的产物6-溴-7-甲基-5-(哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(310mg,83%)。

[1061] (4-(4-氨基-6-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-基)(吡咯烷-1-基)甲酮

[1062] 

[1063] 步骤5:向圆底烧瓶中装入6-溴-7-甲基-5-(哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(280mg,902μmol)、DIEA(580mg,4.50mmol)、DCM(10mL)及搅拌棒。添加三光气(106mg,360μmol),且在室温下搅拌溶液1小时,然后添加吡咯烷(512mg,7.21mmol)且在室温下搅拌1小时。移除溶剂且通过C18 Flash纯化粗产物,得到呈灰白色固体状的6-溴-7-甲基-5-[1-(吡咯烷-1-羰基)哌啶-4-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(160mg,21%)。

[1064] N-(4-(4-氨基-7-甲基-5-(1-(吡咯烷-1-羰基)哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

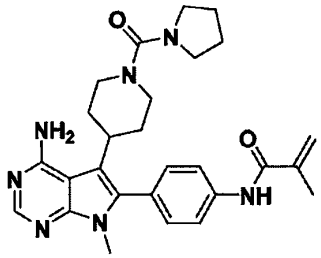
[1065] 

[1066] 步骤6:向可再密封的反应瓶中装入6-溴-7-甲基-5-[1-(吡咯烷-1-羰基)哌啶-4-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(140mg,0.34mmol)、N-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)丙烯酰胺(112mg,0.41mmol)、$Pd(dppf)Cl_2$(25.1mg,34.3μmol)、K_3PO_4(216mg,1.02mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF(1mL)及H2O(0.1mL),且在90℃下搅拌混合物3小时。所得混合物经由C18柱纯化。所得粗物质通过HPLC纯化。冻干产生呈白色无定形固体状的N-(4-{4-氨基-7-甲基-5-[1-(吡咯烷-1-羰基)哌啶-4-基]-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺(24.3mg,15%)。

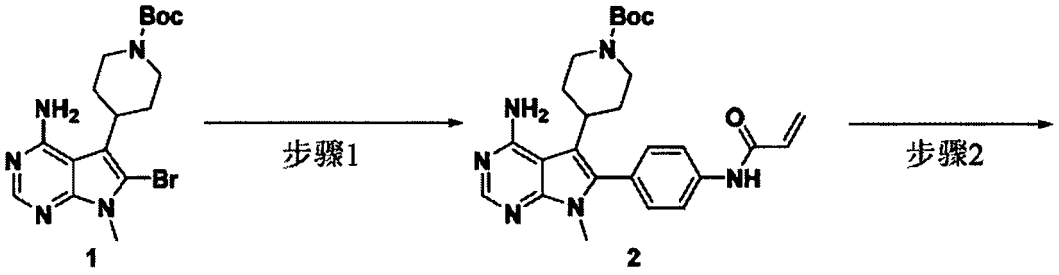
[1067] 根据实例5的方法制备的其它化合物描绘于下表4中。

[1068] 表4.示例性化合物

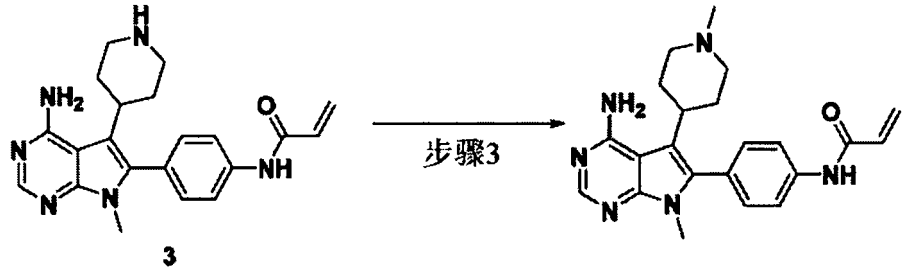
[1069]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-(吡咯烷-1-羰基)哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.11 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 6.38 (s, 2H), 5.83 (s, 1H), 5.56 (s, 1H), 3.58 - 3.61 (m, 2H), 3.55 (s, 3H), 3.26 - 3.38 (m, 4H), 3.02 - 3.05 (m, 1H), 2.68 - 2.76 (m, 2H), 2.08 (s, 3H), 1.63 - 1.66 (m, 4H), 1.48 - 1.57 (m, 4H).	488.3

[1070] 流程4



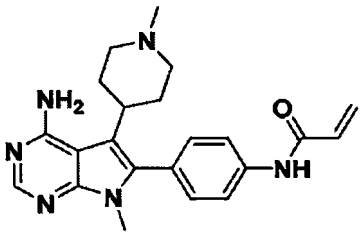
[1071]



[1072] 实例6

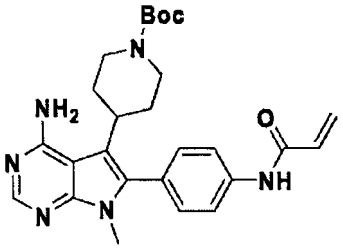
[1073] N-(4-(4-氨基-7-甲基-5-(1-甲基哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺

[1074]



[1075] 4-(6-(4-丙烯酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯

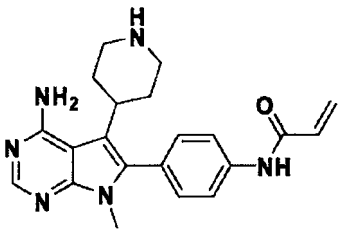
[1076]



[1077] 步骤1:向圆底烧瓶中装入4-(4-氨基-6-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-

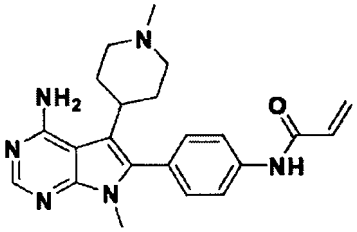
基)哌啶-1-甲酸叔丁酯(700mg,1.7mmol)、N-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)丙烯酰胺(559mg,2.0mmol)、Pd(dtbpf)Cl2(124mg,0.17mmol)、K_3PO_4(1.08g,5.1mmol)及搅拌棒。添加DMF(10mL)及H_2O(1mL),且在90℃下搅拌溶液3小时。混合物用EtOAc(100mL)稀释且用水(3*100mL)洗涤,且浓缩有机相且通过使用DCM:MeOH=25:1的硅胶柱纯化粗产物,得到呈黄色固体状的4-(6-(4-丙烯酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯(340mg,42%)。

[1078] 4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯

[1079] 

[1080] 步骤2:向圆底烧瓶中装入4-(6-(4-丙烯酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯(340mg,0.71mmol)、DCM(5mL)及搅拌棒。添加TFA(0.5mL),且在25℃下搅拌溶液2小时。在减压下浓缩混合物,且用DCM(30mL)稀释,用$NaHCO_3$饱和水溶液(3*15mL)洗涤,浓缩有机相且获得呈棕色油状的产物4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯(240mg,89%)。

[1081] N-(4-(4-氨基-7-甲基-5-(1-甲基哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺

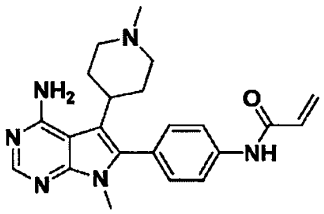
[1082] 

[1083] 步骤3:向圆底烧瓶中装入4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)哌啶-1-甲酸叔丁酯(120mg,0.32mmol)、$NaBH(OAc)_3$(81mg,0.38mmol)、$(CH_2O)_n$(20mg,0.64mmol)及搅拌棒。添加DCM(5mL)及AcOH(0.5mL),且在室温下搅拌溶液整夜。反应混合物用水(50mL)稀释,且水相用DCM(20mL)萃取三次。合并的有机层经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化。冻干产生呈白色无定形固体状的N-(4-{4-氨基-7-甲基-5-[1-(吡咯烷-1-羰基)哌啶-4-基]-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺(8mg,6%)。

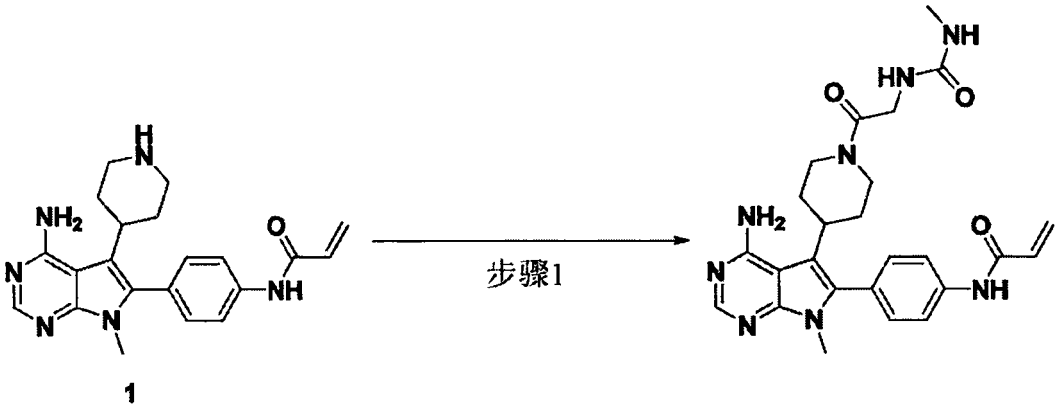
[1084] 根据实例6的方法制备的其它化合物描绘于下表5中。

[1085] 表5.示例性化合物

[1086]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-甲基哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 8.11 (s, 1H), 7.85 - 7.78 (m, 2H), 7.40 - 7.29 (m, 2H), 6.49 (dd, J = 17.0, 10.1 Hz, 1H), 6.37-6.28 (m, 3H), 5.81 (dd, J = 10.0, 2.0 Hz, 1H), 3.37 (s, 3H), 2.75 (d, J = 10.9 Hz, 3H), 2.50-2.31 (m, 3H), 2.14 (s, 3H), 1.93-1.91 (m, 2H), 1.65 (s, 4H).	391.2

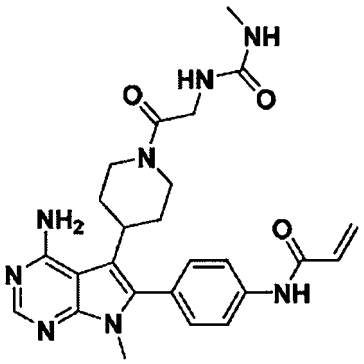
[1087] 流程5

[1088] 

1

[1089] 实例7

[1090] N-(4-(4-氨基-7-甲基-5-(1-((甲基胺甲酰基)甘胺酰基)哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺

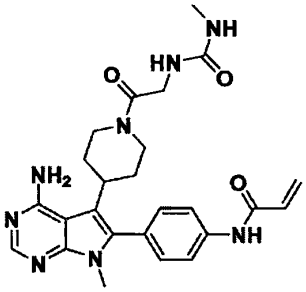
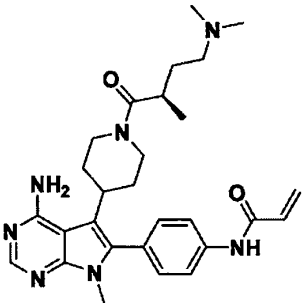
[1091] 

[1092] 向可再密封的反应瓶中装入N-{4-[4-氨基-7-甲基-5-(哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}丙-2-烯酰胺(100mg,0.265mmol)、2-[(甲基胺甲酰基)氨基]乙酸(35.0mg,0.265mmol)、HATU(121mg,0.32mmol)、DIEA(68.5mg,0.53mmmol)及搅拌棒。添加二甲基甲酰胺(5mL),且在室温下搅拌混合物1小时。反应混合物用水(10mL)稀释,且水相用二氯甲烷(15mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(乙腈/水/0.1%甲酸)。冻干产生呈白色无定形固体状的N-{4-[4-氨基-7-甲基-5-(1-{2-[(甲基胺甲酰基)氨基]乙酰基}哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}丙-2-烯酰胺(6.00mg,5%)。

[1093] 根据实例7的方法制备的其它化合物描绘于下表6中。

[1094] 表6.其它示例性化合物

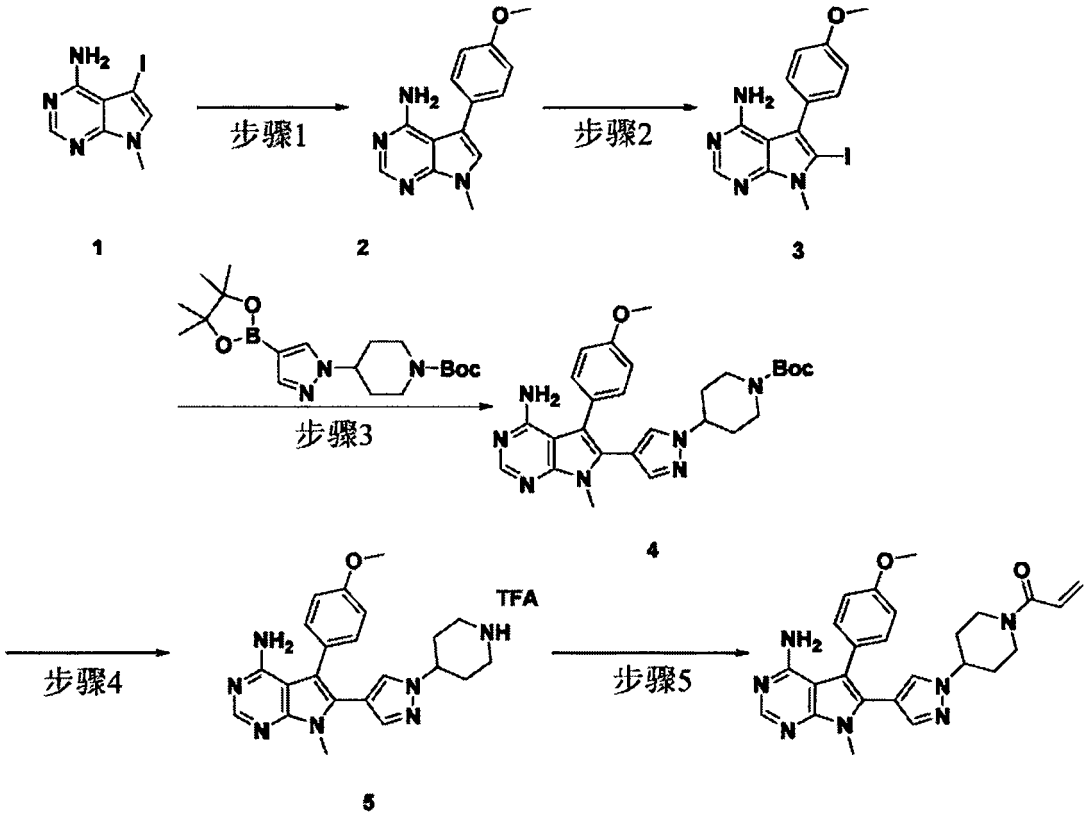
[1095]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-((甲基胺甲酰基)甘胺酰基)哌啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 8.10 (s, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 6.47 (dd, J = 17.0, 10.2 Hz, 1H), 6.39 (s, 2H), 6.30 (d, J = 16.8 Hz, 1H), 6.10 (s, 1H), 5.92 (s, 1H), 5.80 (d, J = 10.5 Hz, 1H), 3.78-3.66 (m, 3H), 3.45-3.37 (m, 1H), 3.31 (s, 3H), 3.21-3.08 (m, 2H), 2.55-2.53 (m, 1H), 2.51 (s, 3H), 1.86-1.73 (m, 2H), 1.45-1.24 (m, 2H).	491.2
(R)-N-(4-(4-氨基-5-(1-(4-(二甲基氨基)-2-甲基丁酰基)哌啶-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.31 (s, 1H), 8.10 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 6.53 - 6.42 (m, 3H), 6.30 (dd, J = 16.8, 2.1 Hz, 1H), 5.80 (dd, J = 10.0, 2.0 Hz, 1H), 4.37 (s, 1H), 3.88 (s, 1H), 3.28 (s, 3H), 3.09 (t, J = 13.6 Hz, 1H), 2.75-2.61 (m, 2H), 2.06 (s, 4H), 2.01 (s, 4H), 1.76-1.48 (m, 4H), 1.29-1.22 (m, 3H), 0.91-0.82 (m, 3H).	504.4

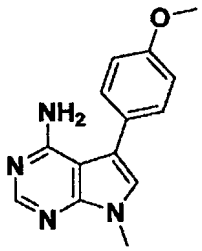
[1096] 实例8

[1097] 流程6

[1098]

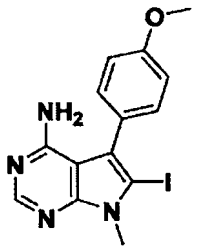


[1099] 5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1100] 

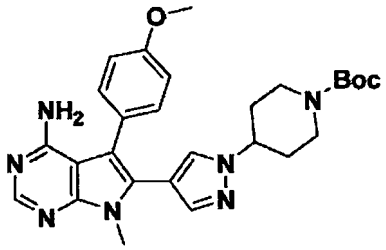
[1101] 步骤1:向可再密封的反应瓶中装入5-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(20g,72.9mmol)、(4-甲氧基苯基)硼酸(13.3g,87.5mmol)、Pd(DtBPF)Cl_2(4.74g,7.29mmol)、CsF(33.1g,218mmol)、DMF(200mL)、H_2O(25mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物1小时。反应混合物用H_2O(500mL)稀释,且水相用DCM(200mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。向反应混合物中添加MeCN(10mL)且经由**Celite®**垫过滤,用MeCN洗涤垫。真空浓缩滤液且所得固体为5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(10.2g,55%),以黄色无定形固体状获得。

[1102] 6-碘-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1103] 

[1104] 步骤2:向圆底烧瓶中装入5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(9.8g,38.5mmol)、DCM(200mL)、TFA(13.1g,115mmol)及搅拌棒。将混合物冷却至0℃,添加NIS(9.53g,42.4mmol),且在室温下搅拌溶液1小时。反应混合物用Na_2SO_3溶液稀释,且水相用DCM(300mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。添加DCM(20mL)且经由**Celite®**垫过滤反应混合物,用少量DCM洗涤垫。真空浓缩滤液且所得固体为6-碘-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(10.9g,74%),以灰白色无定形固体呈状获得。

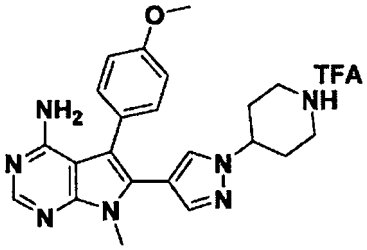
[1105] 4-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯

[1106] 

[1107] 步骤3:向可再密封的反应瓶中装入6-碘-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(1g,2.63mmol)、4-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯(1.2g,3.16mmol)、Pd(dppf)Cl_2(190mg,0.26mmol)、K_3PO_4(1.5g,6.9mmol)、DMF(20mL)、H_2O(2mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物1小时。反应混合物用H_2O(100mL)稀释,且水相用DCM(100mL)

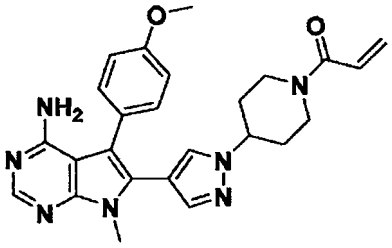
萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用MeOH/DCM=1/40洗脱)纯化。真空浓缩以产生呈黄色固体状的4-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯(800mg,61%)。

[1108] 5-(4-甲氧基苯基)-7-甲基-6-(1(哌啶-4-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺三氟乙酸盐

[1109] 

[1110] 步骤4:向圆底烧瓶中装入4-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯(800mg,1.6mmol)、DCM(20mL)及搅拌棒。添加TFA(5mL)。在室温下搅拌反应混合物1小时。真空移除溶剂以产生呈深色油状的5-(4-甲氧基苯基)-7-甲基-6-(1-(哌啶-4-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺三氟乙酸盐(795mg,100%)。

[1111] 1-(4-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮

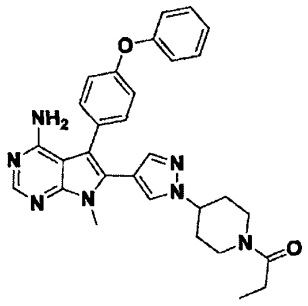
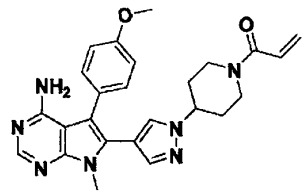
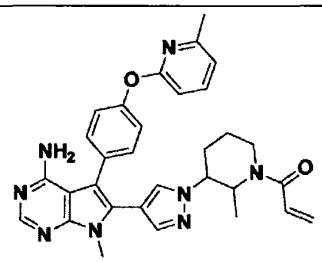
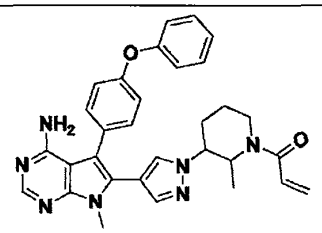
[1112] 

[1113] 步骤5:向圆底烧瓶中装入5-(4-甲氧基苯基)-7-甲基-6-(1-(哌啶-4-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺三氟乙酸盐(120mg,0.24mmol)、Et_3N(72.9mg,0.72mmol)、DCM(10mL)及搅拌棒。将混合物冷却至-30℃,逐滴添加丙-2-烯酰氯(21.6mg,0.24mmol)且在-30℃下搅拌溶液0.5小时。反应混合物用MeOH骤冷且真空浓缩。所得粗物质通过制备型HPLC纯化。冻干以产生呈白色无定形固体状的1-(4-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮(33mg,30%)。

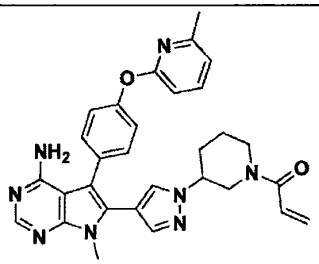
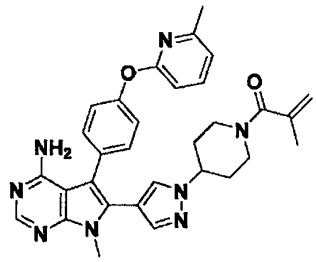
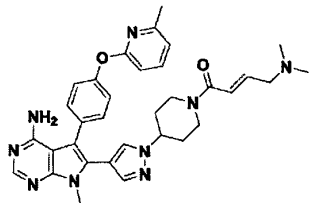
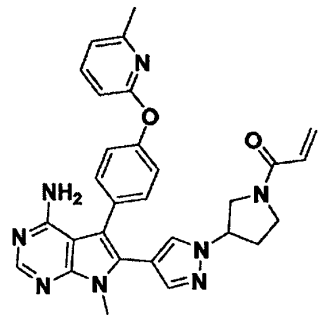
[1114] 根据实例8的方法制备的其它化合物描绘于下表7中。

[1115] 表7.其它示例性化合物

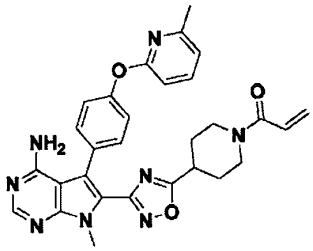
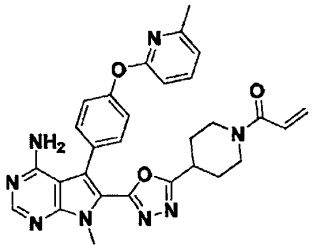
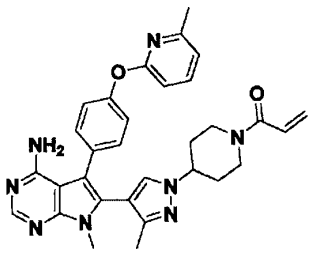
[1116]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-7-甲基-5-(4-苯氧基苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 1.63 - 1.88 (m, 2H), 2.01 (t, J = 14.8 Hz, 2H), 2.35 (q, J = 7.6 Hz, 2H), 2.73 (t, J = 12.4 Hz, 1H), 3.16 (t, J = 12.8 Hz, 1H), 3.70 (s, 3H), 3.93 (d, J = 14.0 Hz, 1H), 4.43 (td, J = 5.6, 11.5 Hz, 2H), 5.85 (s, 1H), 7.02 - 7.07 (m, 2H), 7.07 - 7.12 (m, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.27 - 7.35 (m, 2H), 7.39 - 7.46 (m, 3H), 7.89 (s, 1H), 8.15 (s, 1H).	522.23
1-(4-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.18 (s, 1H), 7.95 (s, 1H), 7.36 (s, 1H), 7.29 - 7.21 (m, 2H), 7.04 - 6.96 (m, 2H), 6.85 (m, 1H), 6.12 (m, 1H), 5.70 (m, 1H), 4.47 (t, J = 7.2 Hz, 2H), 4.13 (d, J = 13.6 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.24 (d, J = 13.6 Hz, 1H), 2.83 (t, J = 12.4 Hz, 1H), 2.04 (d, J = 12.4 Hz, 2H), 1.79 (d, J = 16.8 Hz, 2H).	458.22
1-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)-2-甲基哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.77 (s, 1H), 7.80 - 7.72 (m, 1H), 7.48 (s, 1H), 7.38 - 7.25 (m, 2H), 7.16 - 7.10 (m, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.66 (s, 1H), 6.01 (d, J = 16.4 Hz, 1H), 5.60 (d, J = 10.4 Hz, 1H), 5.01 (s, 1H), 4.38 (s, 1H), 4.07 (s, 1H), 3.66 (s, 3H), 3.32 (s, 1H), 3.07 (s, 1H), 2.37 (s, 3H), 2.15 (s, 2H), 1.49 (s, 1H), 1.38 (s, 1H), 1.31 (d, J = 6.8 Hz, 3H).	549.25
1-(3-(4-(4-氨基-7-甲基-5-(4-苯氧基苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)-2-甲基哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.77 (s, 1H), 7.80 - 7.72 (m, 1H), 7.48 (s, 1H), 7.38 - 7.25 (m, 2H), 7.16 - 7.10 (m, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.66 (s, 1H), 6.01 (d, J = 16.4 Hz, 1H), 5.60 (d, J = 10.4 Hz, 1H), 5.01 (s, 1H), 4.38 (s, 1H), 4.07 (s, 1H), 3.66 (s, 3H), 3.32 (s, 1H), 3.07 (s, 1H), 2.15 (s, 2H), 1.49 (s, 1H), 1.38 (s, 1H), 1.31 (d, J = 6.8 Hz, 3H).	534.25

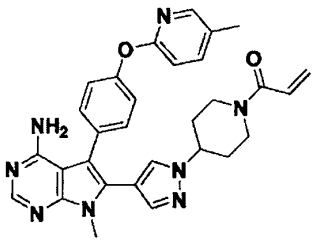
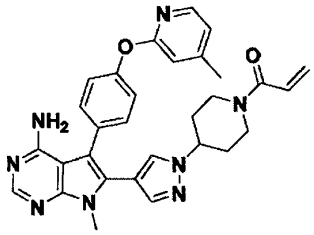
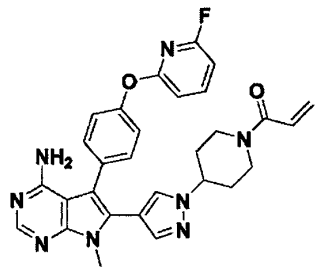
[1117]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.16 (s, 1H), 7.96 (s, 1H), 7.79 - 7.71 (m, 1H), 7.47 (s, 1H), 7.38 - 7.31 (m, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 7.2 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 6.38 - 5.91 (m, 1H), 5.67 (dd, J = 10.4, 32.3 Hz, 1H), 4.51 - 3.93 (m, 3H), 3.70 (s, 3H), 3.56 (s, 0H), 3.17 (s, 1H), 2.98 (s, 0H), 2.36 (s, 3H), 2.09 (d, J = 17.2 Hz, 2H), 1.77 (s, 1H), 1.50 (s, 1H).	535.25
1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)-2-甲基丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.16 (s, 1H), 7.95 (s, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.17 (s, 1H), 5.00 (s, 1H), 4.46 (t, J = 11.6 Hz, 1H), 3.94 (s, 1H), 3.70 (s, 3H), 2.84 (s, 1H), 2.35 (s, 3H), 2.04 (d, J = 12.8 Hz, 2H), 1.86 (s, 3H), 1.79 (d, J = 12.8 Hz, 2H).	549.26
(E)-1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)-4-(二甲基氨基)丁-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.15 (s, 1H), 7.95 (s, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 2.8 Hz, 2H), 4.45 (s, 2H), 4.13 (s, 1H), 3.69 (s, 3H), 3.02 (d, J = 4.0 Hz, 2H), 2.80 (s, 2H), 2.35 (s, 3H), 2.14 (s, 6H), 2.03 (s, 2H), 1.78 (s, 3H).	592.41
1-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.16 (s, 1H), 7.98 (d, J = 18.1 Hz, 1H), 7.78 - 7.75 (m, 1H), 7.50 - 7.44 (m, 1H), 7.37 - 7.30 (m, 2H), 7.14 (dd, J = 8.6, 1.9 Hz, 2H), 7.03 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.57 (dt, J = 16.7, 10.6 Hz, 1H), 6.14 (ddd, J = 16.7, 5.5, 2.4 Hz, 1H), 5.66 (ddd, J = 12.8, 10.3, 2.4 Hz, 1H), 5.09 - 4.96 (m, 1H), 3.92 - 3.78 (m, 1H), 3.70 (s, 5H), 3.62 - 3.42 (m, 3H), 2.36 (s, 4H).	521.20

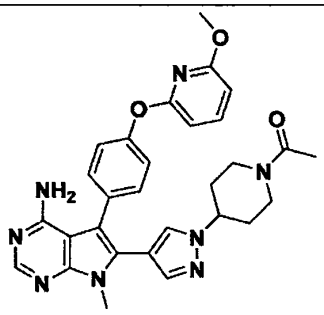
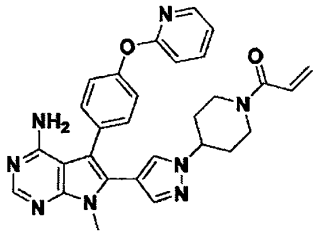
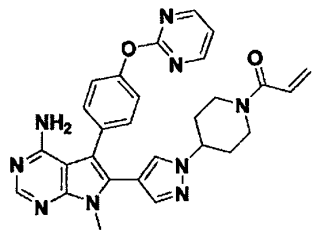
[1118]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1,2,4-恶二唑-5-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.79 (dd, J = 17.3, 9.7 Hz, 2H), 6.09 (dd, J = 16.6, 2.5 Hz, 1H), 5.66 (dd, J = 10.3, 2.5 Hz, 1H), 4.15 (d, J = 13.0 Hz, 1H), 3.92 (s, 2H), 3.22 (d, J = 45.6 Hz, 4H), 3.03 (d, J = 12.4 Hz, 1H), 2.37 (s, 3H), 2.12 - 1.96 (m, 2H), 1.64 (s, 2H).	537.40
1-(4-(5-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1,3,4-恶二唑-2-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 - 1.68 (m, 2H), 1.80 - 1.92 (m, 2H), 2.38 (s, 3H), 2.92 - 3.00 (m, 1H), 3.10 - 3.26 (m, 2H), 3.85 - 3.98 (m, 1H), 4.04 (s, 3H), 4.04 - 4.09 (m, 1H), 5.63 (dd, J = 2.8 Hz, 1H), 6.07 (dd, J = 2.4 Hz, 1H), 6.70 - 6.77 (m, 1H), 6.83 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 7.24 (d, J = 11.2 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.79 (t, J = 15.6 Hz, 1H), 8.28 (s, 1H)	537.40
1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.01 (s, 1H), 7.77 - 7.70 (m, 1H), 7.25 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.89 - 6.75 (m, 2H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.71 - 5.66 (m, 1H), 4.49 (d, J = 12.4 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 4.14 (d, J = 13.5 Hz, 1H), 3.55 (s, 3H), 3.32 (s, 2H), 3.23 (s, 1H), 2.83 (t, J = 13.1 Hz, 1H), 2.34 (s, 3H), 2.07 (d, J = 10.1 Hz, 2H), 1.88 - 1.75 (m, 2H), 1.70 (s, 3H).	549.40

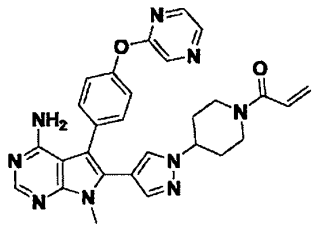
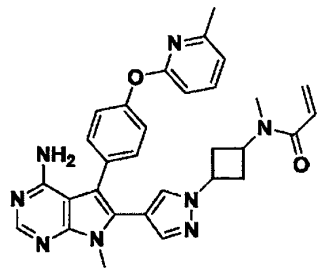
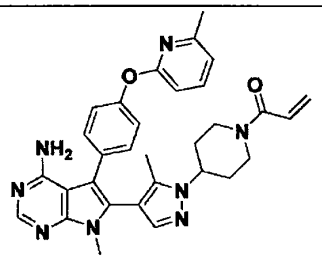
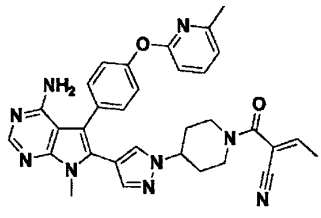
[1119]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-7-甲基-5-(4-((5-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.16 (s, 1H), 8.03 (dd, J = 2.1, 1.1 Hz, 1H), 7.94 (d, J = 0.7 Hz, 1H), 7.71 (dd, J = 8.2, 2.5 Hz, 1H), 7.45 (d, J = 0.7 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.17 - 7.09 (m, 2H), 6.99 (d, J = 8.3 Hz, 1H), 6.85 (dd, J = 16.7, 10.4 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.69 (dd, J = 10.4, 2.4 Hz, 1H), 4.51 - 4.41 (m, 2H), 4.14 (d, J = 13.9 Hz, 1H), 3.70 (s, 3H), 3.23 (t, J = 12.9 Hz, 1H), 2.84 (t, J = 12.5 Hz, 1H), 2.27 (s, 3H), 2.04 (s, 2H), 1.78 (t, J = 13.6 Hz, 2H).	535.3
1-(4-(4-(4-氨基-7-甲基-5-(4-((4-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 8.05 (d, *J* = 5.2 Hz, 1H), 7.95 (s, 1H), 7.45 (s, 1H), 7.36 - 7.31 (m, 2H), 7.16 - 7.12 (m, 2H), 7.02 - 6.99 (m, 1H), 6.91 (s, 1H), 6.85 (dd, *J* = 16.7, 10.5 Hz, 1H), 6.12 (dd, *J* = 16.7, 2.5 Hz, 1H), 5.69 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.46 (t, *J* = 10.8 Hz, 1H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.70 (s, 3H), 3.21 (d, *J* = 12.9 Hz, 1H), 2.83 (t, *J* = 12.6 Hz, 1H), 2.35 (s, 4H), 2.04 (s, 2H), 1.80 (d, *J* = 13.6 Hz, 2H).	535.40
1-(4-(4-(4-氨基-5-(4-((6-氟吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.17 (s, 1H), 8.05 (q, J = 8.1 Hz, 1H), 7.92 (s, 1H), 7.46 (s, 1H), 7.42 - 7.34 (m, 2H), 7.27 - 7.19 (m, 2H), 6.97 (dd, J = 7.9, 1.7 Hz, 1H), 6.92 (dd, J = 7.9, 2.4 Hz, 1H), 6.84 (dd, J = 16.7, 10.5 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.85 (s, 2H), 5.69 (dd, J = 10.4, 2.4 Hz, 1H), 4.46 (ddd, J = 15.3, 11.3, 3.9 Hz, 1H), 4.14 (d, J = 13.8 Hz, 1H), 3.70 (s, 3H), 3.22 (t, J = 12.9 Hz, 1H), 2.83 (t, J = 12.6 Hz, 1H), 2.05 (d, J = 12.4 Hz, 2H), 1.79 (t, J = 12.8 Hz, 2H).	539.3

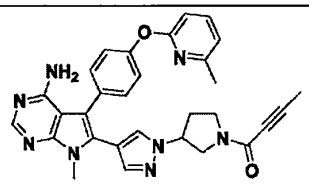
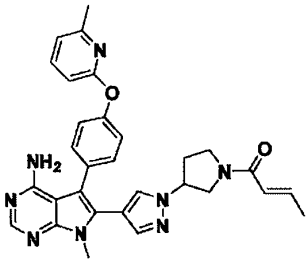
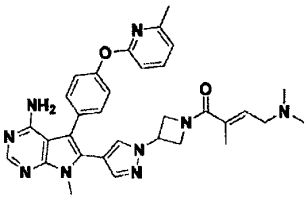
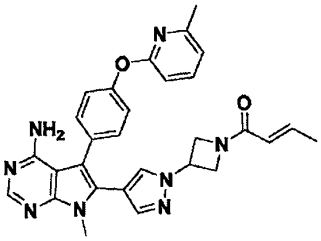
[1120]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-5-(4-((6-甲氧基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)乙-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.98 (s, 1H), 7.76 (t, J = 7.9 Hz, 1H), 7.41 - 7.30 (m, 3H), 7.25 - 7.16 (m, 2H), 6.85 (dd, J = 16.7, 10.4 Hz, 1H), 6.55 (dd, J = 7.9, 5.0 Hz, 2H), 6.12 (dd, J = 16.6, 2.5 Hz, 1H), 5.69 (dd, J = 10.5, 2.4 Hz, 1H), 4.47 (td, J = 12.2, 11.3, 6.8 Hz, 2H), 4.14 (d, J = 13.6 Hz, 1H), 3.69 (d, J = 15.3 Hz, 6H), 3.21 (d, J = 13.0 Hz, 1H), 2.83 (t, J = 12.6 Hz, 1H), 2.04 (d, J = 12.5 Hz, 2H), 1.89 - 1.65 (m, 2H).	551.35
1-(4-(4-(4-氨基-7-甲基-5-(4-(吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 - 8.13 (m, 2H), 7.94 (s, 1H), 7.88 (ddd, J = 8.2, 7.2, 2.0 Hz, 1H), 7.46 (s, 1H), 7.38 - 7.30 (m, 2H), 7.22 - 7.11 (m, 3H), 7.07 (dd, J = 8.3, 1.0 Hz, 1H), 6.84 (dd, J = 16.7, 10.5 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.86 (s, 1H), 5.69 (dd, J = 10.5, 2.4 Hz, 1H), 4.47 (td, J = 11.1, 5.5 Hz, 2H), 4.14 (d, J = 13.8 Hz, 1H), 3.70 (s, 3H), 3.23 (t, J = 12.9 Hz, 1H), 2.83 (t, J = 12.7 Hz, 1H), 2.12 - 1.98 (m, 2H), 1.78 (t, J = 12.9 Hz, 2H).	521.35
1-(4-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.68 (d, J = 4.8 Hz, 2H), 8.17 (s, 1H), 7.96 (s, 1H), 7.48 (d, J = 0.7 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.34 - 7.23 (m, 3H), 6.85 (dd, J = 16.7, 10.5 Hz, 1H), 6.13 (dd, J = 16.6, 2.4 Hz, 1H), 5.70 (dd, J = 10.4, 2.4 Hz, 1H), 4.49 (d, J = 12.4 Hz, 2H), 4.15 (d, J = 13.7 Hz, 1H), 3.70 (s, 3H), 3.24 (s, 1H), 2.84 (t, J = 12.3 Hz, 1H), 2.07 (d, J = 12.4 Hz, 2H), 1.81 (d, J = 14.3 Hz, 2H).	522.2

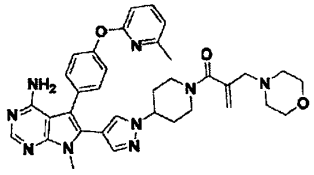
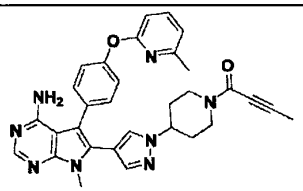
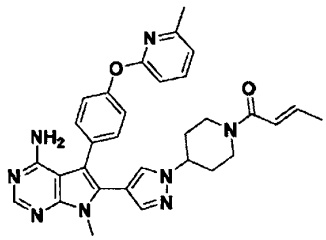
[1121]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-7-甲基-5-(4-(吡嗪-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.58 (d, J = 1.4 Hz, 1H), 8.41 (d, J = 2.7 Hz, 1H), 8.26 (dd, J = 2.7, 1.4 Hz, 1H), 8.17 (s, 1H), 7.94 (d, J = 0.7 Hz, 1H), 7.46 (d, J = 0.7 Hz, 1H), 7.42 - 7.35 (m, 2H), 7.31 - 7.23 (m, 2H), 6.85 (dd, J = 16.7, 10.4 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.69 (dd, J = 10.5, 2.4 Hz, 1H), 4.47 (m, 2H), 4.14 (d, J = 13.5 Hz, 1H), 3.70 (s, 3H), 3.23 (t, J = 12.9 Hz, 1H), 2.84 (t, J = 12.8 Hz, 1H), 2.04 (s, 2H), 1.80 (d, J = 13.6 Hz, 2H).	522.2
N-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)环丁基)-N-甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 8.17 (d, J = 1.4 Hz, 1H), 8.02 (s, 1H), 7.75 (td, J = 7.7, 2.3 Hz, 1H), 7.50 (d, J = 12.4 Hz, 1H), 7.36 (dd, J = 8.7, 2.6 Hz, 2H), 7.18 - 7.14 (m, 2H), 7.04 - 7.00 (m, 1H), 6.82 (dd, J = 8.1, 3.2 Hz, 1H), 6.19 - 5.57 (m, 3H), 5.14 (d, J = 106.7 Hz, 1H), 4.90 (dt, J = 9.0, 4.8 Hz, 1H) 3.71 (d, J = 2.7 Hz, 3H), 3.16 - 2.91 (m, 3H), 2.90 - 2.54 (m, 6H), 2.35 (s, 3H).	535.40
1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-5-甲基-1H-吡唑-1-基)哌啶-1-		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 7.4 Hz, 1H), 6.85 (dd, J = 16.8, 10.6 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.12 (dd, J = 16.8, 2.4 Hz, 1H), 6.01 (s, 2H), 5.69 (dd, J = 10.4, 2.4 Hz, 1H), 4.50 (d, J = 13.2 Hz, 1H), 4.40 (s, 1H), 4.16 (d, J = 13.6 Hz, 1H), 3.58 (s, 3H), 3.20 (t, J = 12.2 Hz, 1H), 2.79 (s, 1H), 2.35 (s, 3H), 1.83 (s, 4H), 1.78 (s, 3H).	549.25
(E)-2-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-羰基)丁-2-烯腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 - 1.93 (m, 3H), 2.07 - 2.09 (m, 5H), 2.25 - 2.36 (m, 5 H), 2.80 - 3.08 (br, 1H), 3.70 (s, 3H), 3.82 - 4.70 (m, 3H), 5.50 - 6.10 (br, 1 H), 6.69 - 6.92 (m, 1H), 6.92 - 7.16 (m, 4H), 7.33 - 7.36 (m , 2H), 7.45 (s, 1H), 7.72 - 7.80 (m, 1H), 7.97 (s, 1H), 8.10 (s, 1H).	574.40

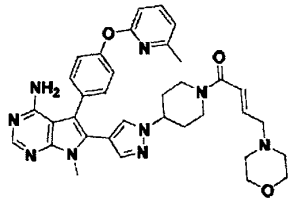
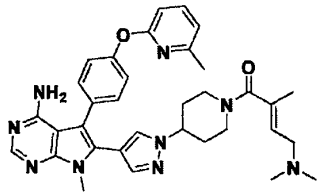
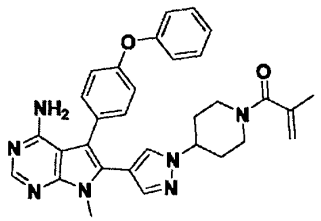
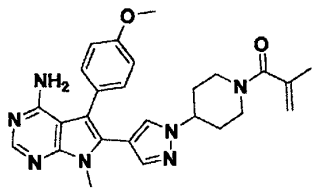
[1122]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)吡咯烷-1-基)丁-2-炔-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 2.00 (d, J = 14.4 Hz, 3H), 2.36 (s, 5H), 3.31 (s, 1H), 3.49 (m, 1H), 3.62 - 3.80 (m, 5H), 3.88 - 4.05 (m, 1H), 5.04 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.11 - 7.19 (m, 2H), 7.30 - 7.39 (m, 2H), 7.48 (d, J = 2.8 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 9.6 Hz, 1H), 8.17 (d, J = 0.8 Hz, 1H).	533.23
(E)-1-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)吡咯烷-1-基)丁-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 1.82 (m, 3H), 2.36 (s, 5H), 3.51 (m, 1H), 3.70 (s, 4H), 3.80 - 4.05 (m, 1H), 4.95 - 5.11 (m, 1H), 6.25 (m, 1H), 6.64 - 6.73 (m, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 7.11 - 7.18 (m, 2H), 7.34 (m, 2H), 7.48 (d, J = 4.4 Hz, 1H), 7.72 - 7.79 (m, 1H), 7.96 (d, J = 26.4 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H).	535.2
(E)-1-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)氮杂环丁-1-基)-4-(二甲基氨基)-2-甲基丁-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.15 (d, J = 11.3 Hz, 2H), 7.76 (t, J = 7.8 Hz, 1H), 7.51 (s, 1H), 7.40 - 7.32 (m, 2H), 7.20 - 7.12 (m, 2H), 7.03 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.92 (td, J = 6.5, 1.6 Hz, 2H), 5.27 (ddd, J = 13.4, 8.2, 5.2 Hz, 1H), 4.70 - 4.05 (m, 4H), 3.71 (s, 3H), 3.31 (s, 1H), 2.98 (d, J = 6.5 Hz, 2H), 2.36 (s, 3H), 2.14 (s, 6H), 1.75 (d, J = 1.4 Hz, 3H).	578.45
(E)-1-(3-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)氮杂环丁-1-基)丁-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 - 1.84 (m, 4H), 2.36 (s, 1H), 3.71 (s, 1H), 4.12 - 4.19 (m, 1H), 4.31 - 4.58 (m, 2H), 4.61 - 4.69 (m, 1 H), 5.27 - 5.33 (m, 1H), 6.01 - 6.06 (m, 1 H), 6.66 - 6.68 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 2.0 Hz, 2H), 7.35 (dd, *J* = 2.0 Hz, 2H), 7.52 (s, 1H), 7.76 (t, *J* = 15.6 Hz, 1H), 8.13 (s, 1H), 8.17 (s, 1H).	521.20

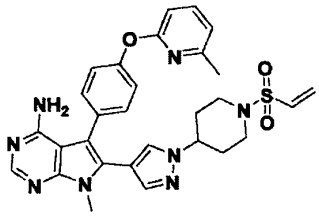
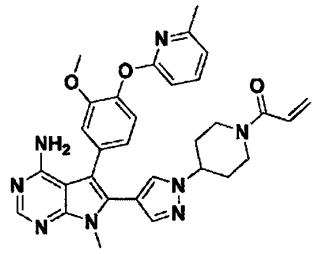
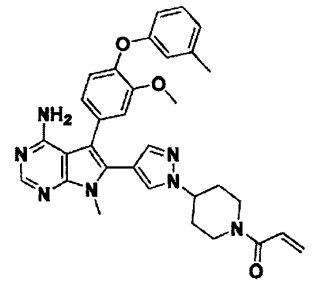
[1123]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)-2-(N-吗啉基甲基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (s, 2H), 2.04 (d, J = 12.5 Hz, 2H), 2.35 (s, 4H), 2.37 (s, 3H), 2.85 (s, 1H), 3.10 (s, 1H), 3.22 (s, 1H), 3.54 (t, J = 4.8 Hz, 4H), 3.70 (s, 3H), 3.98 (s, 1H), 4.38 - 4.51 (m, 2H), 5.20 (s, 1H), 5.35 (s, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 7.12 - 7.18 (m, 2H), 7.32 - 7.38 (m, 2H), 7.47 (d, J = 0.8 Hz, 1H), 7.75 (m, 1H), 7.94 (s, 1H), 8.16 (s, 1H).	634.5
1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丁-2-炔-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 1.73 (m, 1H), 1.86 (m, 1H), 2.03 (s, 4H), 2.10 (d, J = 13.2 Hz, 1H), 2.36 (s, 3H), 2.80 - 2.92 (m, 1H), 3.27 (d, J = 2.8 Hz, 1H), 3.70 (s, 3H), 4.34 (m, 2H), 4.41 - 4.52 (m, 1H), 6.21 (d, J = 273.6 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 7.10 - 7.21 (m, 2H), 7.31 - 7.40 (m, 2H), 7.44 (d, J = 0.7 Hz, 1H), 7.75 (dd, J = 7.3, 8.2 Hz, 1H), 7.97 (s, 1H), 8.16 (s, 1H).	547.25
(E)-1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丁-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.94 (d, J = 0.7 Hz, 1H), 7.75 (dd, J = 8.2, 7.4 Hz, 1H), 7.44 (d, J = 0.7 Hz, 1H), 7.37 - 7.32 (m, 2H), 7.17 - 7.13 (m, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.75 - 6.64 (m, 1H), 6.54 (dd, J = 14.9, 1.7 Hz, 1H), 6.20 - 5.50 (m, 1H), 4.53 - 4.37 (m, 2H), 4.14 (s, 1H), 3.70 (s, 3H), 3.24 - 3.12 (m, 1H), 2.78 (s, 1H), 2.36 (s, 3H), 2.14 - 1.98 (m, 2H), 1.84 (dd, J = 6.7, 1.5 Hz, 3H), 1.77 (s, 2H).	549.25

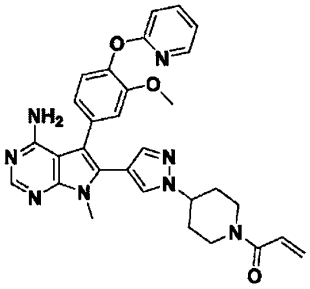
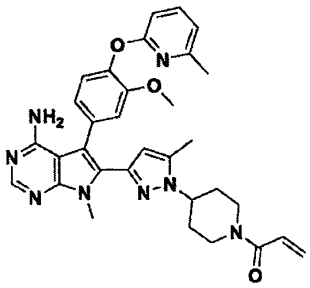
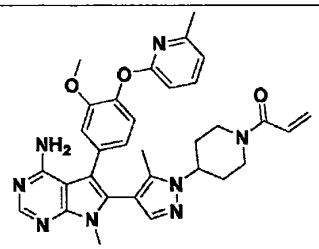
[1124]

化合物	结构	质子 NMR	MS [M+1]
(E)-1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)-4-N-吗啉基丁-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79 (d, J = 18.2=4 Hz, 2H), 2.06 (d, J = 16.0 Hz, 2H), 2.36 (s, 6H), 3.09 (d, J = 5.6 Hz, 4H), 3.58 (t, J = 4.8 Hz, 4H), 3.70 (s, 3H), 4.12 (d, J = 13.6 Hz, 1H), 4.46 (m, 2H), 5.84 (s, 1H), 6.53 - 6.72 (m, 2H), 6.80 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.24 - 7.40 (m, 2H), 7.44 (s, 1H), 7.95 (s, 1H), 8.15 (d, J = 4.4 Hz, 2H)	634.3
(E)-1-(4-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)-4-(二甲基氨基)-2-甲基丁-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.97 (s, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.37 - 7.31 (m, 2H), 7.19 - 7.13 (m, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 5.51 (td, J = 6.6, 1.7 Hz, 2H), 4.60 - 4.33 (m, 1H), 4.38 - 3.79 (m, 1H), 3.70 (s, 3H), 3.34 (s, 1H), 2.93 (d, J = 6.7 Hz, 4H), 2.35 (s, 3H), 2.13 (s, 6H), 2.04 (d, J = 12.7 Hz, 2H), 1.88 - 1.72 (m, 5H).	606.45
1-(4-(4-(4-氨基-7-甲基-5-(4-苯氧基苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)-2-甲基丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.91 (s, 1H), 7.49 - 7.38 (m, 3H), 7.36 - 7.28 (m, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.11 - 7.07 (m, 2H), 7.07 - 7.02 (m, 2H), 5.84 (s, 2H), 5.24 - 5.12 (m, 1H), 5.01 (t, J = 1.3 Hz, 1H), 4.51 - 4.34 (m, 2H), 3.91 (d, J = 28.7 Hz, 1H), 3.70 (s, 3H), 3.22 (s, 1H), 2.86 (s, 1H), 2.04 (d, J = 12.6 Hz, 2H), 1.88 (d, J = 1.4 Hz, 3H), 1.78 (tt, J = 12.2, 6.1 Hz, 2H).	534.40
1-(4-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)-2-甲基丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.94 (s, 1H), 7.36 (s, 1H), 7.28 - 7.22 (m, 2H), 7.07 - 6.90 (m, 2H), 5.76 (s, 2H), 5.26 - 5.14 (m, 1H), 5.01 (t, J = 1.3 Hz, 1H), 4.44 (ddt, J = 11.1, 8.0, 4.0 Hz, 2H), 3.97 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.03 (d, J = 139.1 Hz, 2H), 2.04 (d, J = 12.5 Hz, 2H), 1.88 (d, J = 1.4 Hz, 3H), 1.78 (qd, J = 12.1, 4.4 Hz, 2H).	472.35

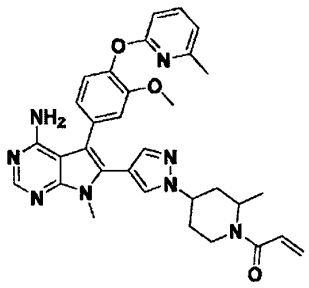
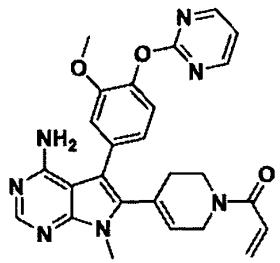
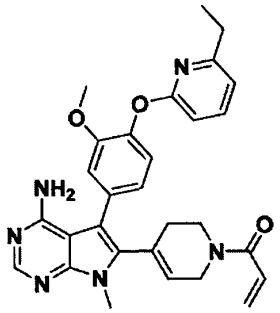
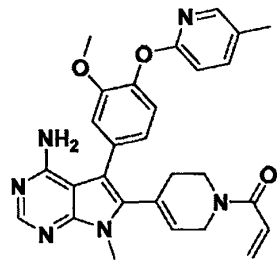
[1125]

化合物	结构	质子 NMR	MS [M+1]
7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-6-(1-(1-(乙烯基磺酰基)哌啶-4-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.97 - 7.94 (m, 1H), 7.75 (dd, J = 8.2, 7.3 Hz, 1H), 7.46 (d, J = 0.7 Hz, 1H), 7.38 - 7.32 (m, 2H), 7.20 - 7.12 (m, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.91 - 6.79 (m, 2H), 6.21 - 6.09 (m, 2H), 5.85 (s, 2H), 4.33 (dt, J = 7.2, 4.1 Hz, 0H), 3.70 (s, 3H), 3.60 (d, J = 12.4 Hz, 2H), 2.84 (td, J = 12.2, 2.7 Hz, 2H), 2.36 (s, 3H), 2.10 (d, J = 12.9 Hz, 2H), 1.95 (qd, J = 12.0, 4.2 Hz, 2H).	571.15
1-(4-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.98 (s, 1H), 7.67 (dd, J = 8.2, 7.4 Hz, 1H), 7.49 (d, J = 0.8 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.97 - 6.90 (m, 2H), 6.85 (dd, J = 16.8, 10.6 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.12 (dd, J = 16.8, 2.6 Hz, 1H), 5.93 (s, 2H), 5.69 (dd, J = 10.6, 2.4 Hz, 1H), 4.54 - 4.43 (m, 2H), 4.15 (d, J = 13.8 Hz, 1H), 3.70 (s, 3H), 3.61 (s, 3H), 3.23 (t, J = 13.4 Hz, 1H), 2.83 (t, J = 12.4 Hz, 1H), 2.32 (s, 3H), 2.06 (d, J = 18.0 Hz, 2H), 1.87 - 1.71 (m, 2H).	565.25
1-(4-(4-(4-氨基-5-(3-甲氧基-4-(间甲苯基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79 (m, 2H), 2.03 (s, 2H), 2.29 (s, 3H), 2.83 (m, 1H), 3.23 (m, 1H), 3.67 (d, J = 20.4 Hz, 6H), 4.14 (d, J = 14.0 Hz, 1H), 4.40 - 4.54 (m, 2H), 5.69 (m, 1H), 6.12 (m, 1H), 6.66 (m, 1H), 6.76 - 6.91 (m, 4H), 7.02 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.95 (s, 1H), 8.16 (s, 1H).	564.45

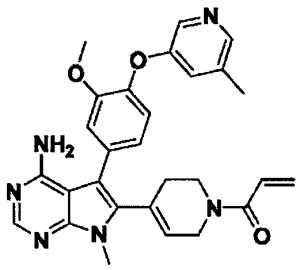
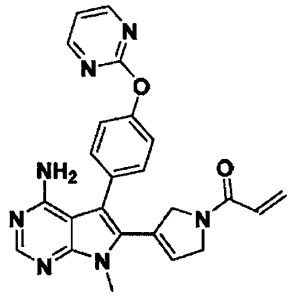
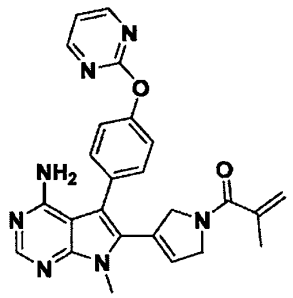
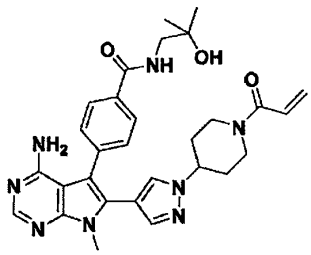
[1126]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-5-(3-甲氧基-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.17 (s, 1H), 8.11 (dd, J = 5.2, 2.0 Hz, 1H), 7.96 (s, 1H), 7.82 (ddd, J = 8.4, 7.2, 2.1 Hz, 1H), 7.52 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.08 (ddd, J = 7.2, 4.9, 0.9 Hz, 1H), 7.03 - 6.92 (m, 3H), 6.85 (dd, J = 16.7, 10.5 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.95 (s, 1H), 5.69 (dd, J = 10.4, 2.4 Hz, 1H), 4.57 - 4.36 (m, 2H), 4.13 (t, J = 11.7 Hz, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.29 - 3.14 (m, 1H), 2.84 (t, J = 12.7 Hz, 1H), 2.05 (s, 2H), 1.79 (t, J = 13.1 Hz, 2H).	551.20
1-(4-(3-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-5-甲基-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 7.00 - 6.92 (m, 2H), 6.84 (dd, J = 16.7, 10.5 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 2H), 5.86 (s, 1H), 5.68 (dd, J = 10.4, 2.5 Hz, 1H), 4.57 - 4.43 (m, 2H), 4.16 (d, J = 13.7 Hz, 1H), 3.84 (s, 3H), 3.63 (s, 3H), 3.25 (d, J = 12.7 Hz, 1H), 2.86 (t, J = 12.0 Hz, 1H), 2.30 (d, J = 17.8 Hz, 6H), 1.90 (d, J = 22.3 Hz, 4H).	579.45
1-(4-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-5-甲基-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.73 - 7.63 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 7.3 Hz, 1H), 6.90 - 6.78 (m, 3H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.12 (dd, *J* = 16.6, 2.4 Hz, 2H), 5.69 (dd, *J* = 10.5, 2.4 Hz, 1H), 4.56 - 4.35 (m, 2H), 4.17 (d, *J* = 13.7 Hz, 1H), 3.60 (s, 3H), 3.47 (s, 3H), 3.20 (t, *J* = 13.1 Hz, 1H), 2.79 (s, 1H), 2.31 (s, 3H), 1.78 (s, 7H).	579.45

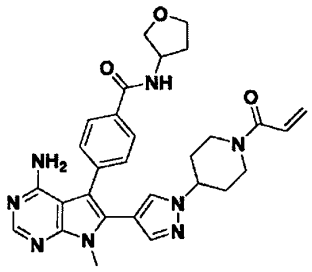
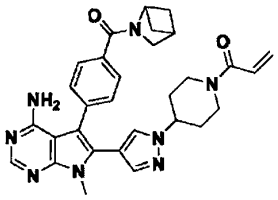
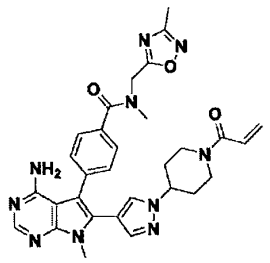
[1127]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)-2-甲基哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 1.3 Hz, 1H), 8.04 (s, 1H), 7.71 - 7.62 (m, 1H), 7.53 (s, 1H), 7.13 (dd, J = 9.2, 8.0 Hz, 1H), 7.04 (dd, J = 6.3, 1.9 Hz, 1H), 6.97 - 6.88 (m, 2H), 6.88 - 6.70 (m, 1H), 6.66 (dd, J = 8.3, 4.5 Hz, 1H), 6.10 (dd, J = 16.6, 2.4 Hz, 1H), 5.95 (s, 1H), 5.72 - 5.62 (m, 1H), 4.46 (s, 1H), 4.06 (s, 1H), 3.69 (s, 3H), 3.62 (d, J = 3.7 Hz, 3H), 2.31 (d, J = 1.9 Hz, 3H), 2.28 - 2.18 (m, 1H), 2.07 (dd, J = 16.7, 8.8 Hz, 2H), 1.32 - 1.18 (m, 1H), 0.84 (d, J = 6.8 Hz, 2H).	578.677
1-(4-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.8 Hz, 2H), 8.17 (s, 1H), 7.30 - 7.22 (m, 2H), 7.10 (s, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.80 (ddd, J = 28.0, 16.6, 10.4 Hz, 1H), 6.31 - 5.87 (m, 3H), 5.69 (t, J = 8.7 Hz, 1H), 4.20 (d, J = 31.7 Hz, 2H), 3.66 (d, J = 5.4 Hz, 8H), 2.18 (s, 2H).	484.25
1-(4-(4-氨基-5-(4-((6-乙基吡啶-2-基)氧基)-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.17 (s, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 6.95 (dd, J = 11.4, 7.8 Hz, 2H), 6.75 (dd, J = 38.1, 9.5 Hz, 2H), 6.38 - 5.84 (m, 3H), 5.69 (t, J = 9.3 Hz, 1H), 4.42 - 4.06 (m, 2H), 3.66 (d, J = 3.1 Hz, 8H), 2.57 (q, J = 7.5 Hz, 2H), 2.18 (s, 2H), 1.08 (t, J = 7.5 Hz, 3H).	511.25
1-(4-(4-氨基-5-(3-甲氧基-4-((5-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.94 (s, 1H), 7.64 (dd, J = 8.5, 2.4 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.07 (s, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.90 - 6.71 (m, 2H), 6.30 - 5.85 (m, 3H), 5.68 (d, J = 9.9 Hz, 1H), 4.20 (d, J = 32.5 Hz, 2H), 3.66 (d, J = 3.5 Hz, 8H), 2.24 (s, 3H), 2.17 (s, 2H).	497.35

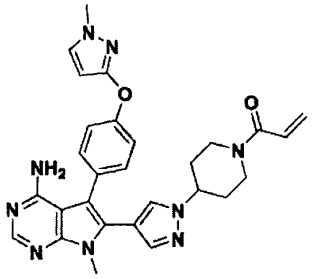
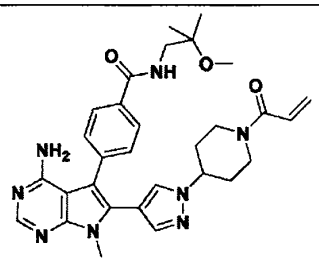
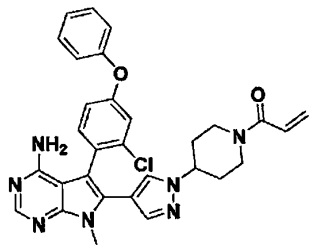
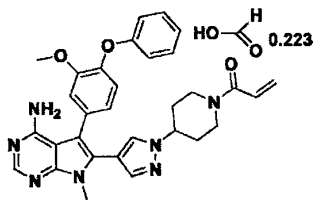
[1128]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-5-(3-甲氧基-4-((5-甲基吡啶-3-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 - 8.07 (m, 3H), 7.18 - 7.08 (m, 3H), 6.96 (dd, J = 8.0, 1.9 Hz, 1H), 6.79 (ddd, J = 26.9, 16.6, 10.4 Hz, 1H), 6.17 - 6.07 (m, 2H), 5.96 (d, J = 18.9 Hz, 1H), 5.74 - 5.64 (m, 1H), 4.19 (d, J = 33.2 Hz, 2H), 3.71 (s, 3H), 3.66 (s, 5H), 2.29 (s, 3H), 2.16 (s, 2H), 2.08 (s, 1H).	497.20
1-(3-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (dd, J = 12.3, 4.7 Hz, 2H), 8.19 (d, J = 1.1 Hz, 1H), 7.51 - 7.41 (m, 2H), 7.38 - 7.27 (m, 3H), 6.62 - 6.25 (m, 2H), 6.15 (dd, J = 16.8, 2.4 Hz, 1H), 5.89 (s, 2H), 5.69 (ddd, J = 14.8, 10.2, 2.4 Hz, 1H), 4.56 (dt, J = 4.8, 2.4 Hz, 1H), 4.35 - 4.22 (m, 2H), 4.05 (q, J = 2.4 Hz, 1H), 3.78 (d, J = 4.1 Hz, 3H).	440.15
1-(3-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基)-2-甲基丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, J = 4.6 Hz, 2H), 8.18 (s, 1H), 7.49 - 7.41 (m, 2H), 7.38 - 7.28 (m, 3H), 6.28 (dd, J = 39.5, 2.3 Hz, 1H), 5.86 (s, 2H), 5.32 - 4.93 (m, 2H), 4.50 - 4.28 (m, 2H), 4.06 (d, J = 10.4 Hz, 2H), 3.79 (d, J = 4.9 Hz, 3H), 1.90 - 1.72 (m, 3H).	454.15
4-(6-(1-(1-丙烯酰基哌啶-4-基)-1H-吡唑-4-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-羟基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (t, J = 6.1 Hz, 1H), 8.18 (s, 1H), 8.00 (s, 1H), 7.92 - 7.81 (m, 2H), 7.43 - 7.35 (m, 3H), 6.84 (dd, J = 16.7, 10.5 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.82 (s, 1H), 5.69 (dd, J = 10.5, 2.4 Hz, 1H), 4.55 (s, 1H), 4.51 - 4.43 (m, 1H), 4.13 (d, J = 13.6 Hz, 1H), 3.69 (s, 3H), 3.27 (d, J = 6.2 Hz, 2H), 2.82 (d, J = 12.1 Hz, 1H), 2.05 (d, J = 12.7 Hz, 2H), 1.79 (s, 2H), 1.12 (s, 6H).	543.35

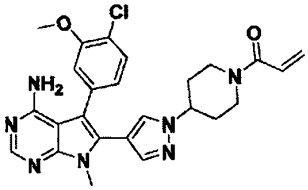
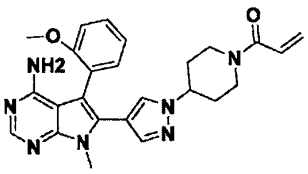
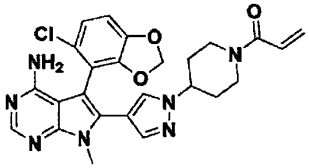
[1129]

化合物	结构	质子 NMR	MS [M+1]
4-(6-(1-(1-丙烯酰基哌啶-4-基)-1H-吡唑-4-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 6.4 Hz, 1H), 8.17 (s, 1H), 8.00 (s, 1H), 7.92 - 7.86 (m, 2H), 7.43 - 7.33 (m, 3H), 6.85 (dd, J = 16.7, 10.5 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.83-5.69 (dd, J = 10.4, 2.4 Hz, 2H), 4.52 - 4.41 (m, 3H), 4.14 (d, J = 13.6 Hz, 1H), 3.87 (dd, J = 8.8, 6.5 Hz, 2H), 3.73 (td, J = 8.1, 5.8 Hz, 1H), 3.68 (s, 3H), 3.59 (dd, J = 8.8, 4.3 Hz, 1H), 3.23 (t, J = 13.1 Hz, 1H), 2.83 (t, J = 12.9 Hz, 1H), 2.16 (dq, J = 12.4, 7.5 Hz, 1H), 2.05 (d, J = 12.4 Hz, 2H), 1.94 (tt, J = 12.4, 5.6 Hz, 1H), 1.78 (d, J = 13.0 Hz, 2H).	541.25
1-(4-(4-(5-(4-(2-氮杂双环[2.1.1]己烷-2-羰基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.92 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.44 - 7.33 (m, 3H), 6.84 (dd, J = 16.7, 10.4 Hz, 1H), 6.12 (dd, J = 16.7, 2.5 Hz, 1H), 5.87 (s, 1H), 5.69 (dd, J = 10.5, 2.4 Hz, 1H), 4.50 - 4.40 (m, 2H), 4.13 (d, J = 13.8 Hz, 1H), 3.69 (s, 3H), 3.47 (s, 2H), 3.32 - 3.17 (m, 1H), 2.89 (s, 1H), 2.81 (d, J = 12.3 Hz, 1H), 2.10 - 1.95 (m, 5H), 1.77 (s, 2H), 1.49 (s, 1H), 1.36 (s, 1H).	537.45
4-(6-(1-(1-丙烯酰基哌啶-4-基)-1H-吡唑-4-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-甲基-N-((3-甲基-1,2,4-恶二唑-5-基)甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.92 (s, 1H), 7.39 (d, J = 14.2 Hz, 5H), 6.84 (dd, J = 16.7, 10.5 Hz, 1H), 6.11 (dd, J = 16.7, 2.4 Hz, 1H), 5.89 (s, 1H), 5.69 (dd, J = 10.5, 2.4 Hz, 1H), 4.94 (s, 2H), 4.45 (s, 2H), 4.12 (d, J = 13.8 Hz, 1H), 3.69 (s, 3H), 3.17 (d, J = 33.9 Hz, 4H), 2.82 (t, J = 12.9 Hz, 1H), 2.37 (s, 3H), 2.05 (d, J = 26.0 Hz, 2H), 1.78 (d, J = 13.9 Hz, 2H).	581.30

[1130]

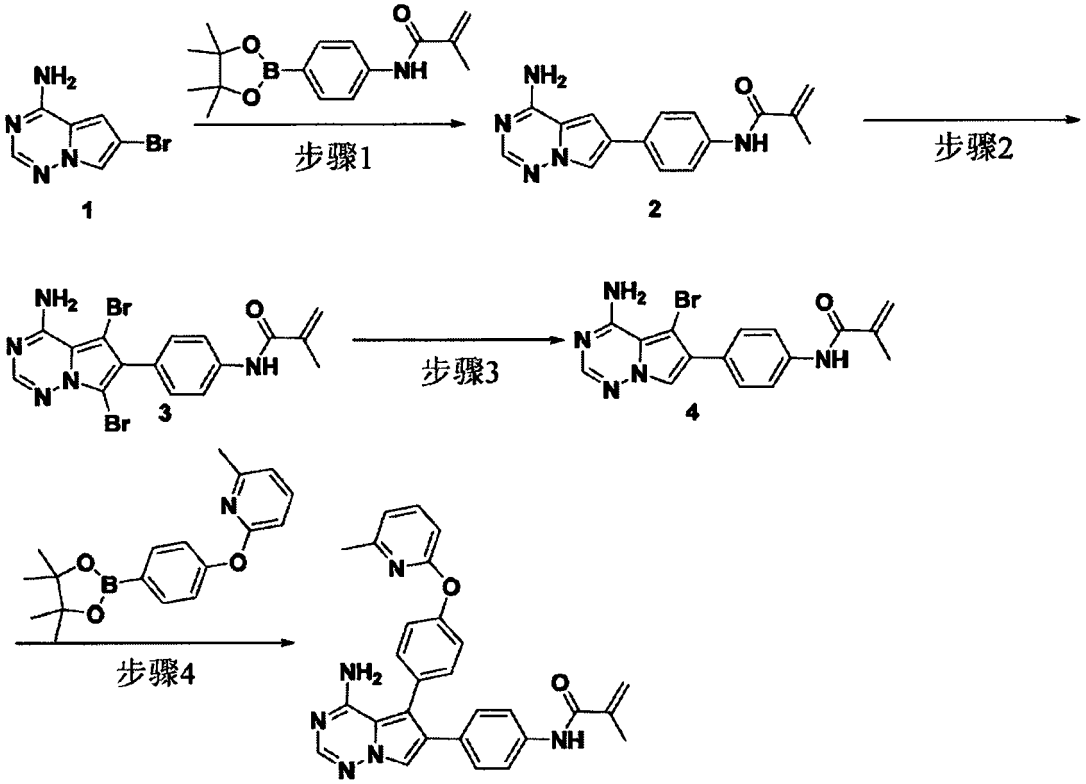
化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-(4-氨基-7-甲基-5-(4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1H-吡唑-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.92 (s, 1H), 7.83 (s, 1H), 7.55 (s, 1H), 7.46 - 7.38 (m, 2H), 7.26 (s, 1H), 7.20 - 7.16 (m, 2H), 6.87 - 6.80 (m, 1H), 6.11 (dd, J = 16.7, 2.4 Hz, 1H), 6.07 - 5.99 (m, 1H), 5.70 - 5.66 (m, 1H), 4.56 - 4.38 (m, 2H), 4.18 - 4.09 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.21 (t, J = 12.7 Hz, 1H), 2.81 (t, J = 12.7 Hz, 1H), 2.02 (d, J = 12.5 Hz, 2H), 1.84 - 1.68 (m, 2H).	524.35
4-(6-(1-(1-丙烯酰基哌啶-4-基)-1H-吡唑-4-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(2-甲氧基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 8.00 (s, 2H), 7.88 (d, J = 7.9 Hz, 2H), 7.43 - 7.35 (m, 3H), 6.84 (dd, J = 16.8, 10.7 Hz, 1H), 6.12 (d, J = 16.6 Hz, 1H), 5.69 (d, J = 10.8 Hz, 2H), 4.48 (d, J = 14.5 Hz, 2H),4.13(s, 1H) 3.68 (s, 3H), 3.40-3.23 (s, 3H), 3.16 (s, 3H), 2.83 (s, 1H), 2.04 (s, 2H), 1.79 (s, 2H), 1.13 (s, 6H).	557.45
1-(4-{4-[4-氨基-5-(2-氯-4-苯氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基]-1H-吡唑-1-基}哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.88 (s, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.28 - 7.14 (m, 4H), 7.00 (dd, J = 8.4, 2.6 Hz, 1H), 6.85 (dd, J = 16.7, 10.4 Hz, 1H), 6.13 (dd, J = 16.8, 2.4 Hz, 1H), 5.77 (s, 2H), 4.47 (tt, J = 11.4, 4.1 Hz, 2H), 4.14 (d, J = 13.7 Hz, 1H), 3.76 (s, 3H), 3.24 (t, J = 12.8 Hz, 1H), 2.85 (t, J = 12.7 Hz, 1H), 2.03 (s, 2H), 1.78 (t, J = 12.6 Hz, 2H).	554.05
1-(4-{4-[4-氨基-5-(3-甲氧基-4-苯氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基]-1H-吡唑-1-基}哌啶-1-基)丙-2-烯-1-酮；甲酸		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.92 (s, 1H), 7.49 (s, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.10 - 7.00 (m, 3H), 7.00 - 6.79 (m, 4H), 6.13 (dd, J = 16.7, 2.4 Hz, 1H), 5.70 (dd, J = 10.4, 2.4 Hz, 1H), 4.49 (tt, J = 11.6, 4.1 Hz, 2H), 4.14 (d, J = 13.8 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.24 (t, J = 12.9 Hz, 1H), 2.85 (t, J = 12.7 Hz, 1H), 2.03 (s, 2H), 1.80 (t, J = 12.6 Hz, 2H).	595.66

[1131]

化合物	结构	质子 NMR	MS [M+1]
1-(4-{4-[4-氨基-5-(4-氯-3-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基]-1H-吡唑-1-基}哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.98 (d, J = 0.8 Hz, 1H), 7.46 - 7.39 (m, 2H), 7.00 (d, J = 1.9 Hz, 1H), 6.91 - 6.85 (m, 1H), 6.89 - 6.80 (m, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 5.92 (s, 2H), 5.70 (dd, J = 10.5, 2.4 Hz, 1H), 4.53 - 4.43 (m, 1H), 4.14 (d, J = 14.0 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.23 (t, J = 13.2 Hz, 1H), 2.84 (t, J = 12.9 Hz, 1H), 2.04 (d, J = 12.8 Hz, 2H), 1.80 (s, 2H).	491.98
1-(4-{4-[4-氨基-5-(2-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基]-1H-吡唑-1-基}哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.87 (s, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.29 (s, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.84 (dd, J = 16.7, 10.5 Hz, 1H), 6.12 (dd, J = 16.5, 2.4 Hz, 1H), 5.69 (dd, J = 10.3, 2.4 Hz, 1H), 5.57 (s, 2H), 4.42 (dt, J = 15.2, 5.3 Hz, 2H), 4.12 (d, J = 13.8 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 2.82 (t, J = 12.9 Hz, 3H), 2.02 (d, J = 12.5 Hz, 2H), 1.81 - 1.70 (m, 2H).	457.538
1-(4-{4-[4-氨基-5-(5-氯-2H-1,3-苯并二唑-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基]-1H-吡唑-1-基}哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.96 (s, 1H), 7.37 (s, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.85 (dd, J = 16.7, 10.5 Hz, 1H), 6.12 (dd, J = 16.7, 2.4 Hz, 1H), 6.01 (d, J = 1.0 Hz, 1H), 5.96 (d, J = 1.0 Hz, 1H), 5.70 (dd, J = 10.5, 2.4 Hz, 1H), 4.53 - 4.43 (m, 2H), 4.13 (d, J = 13.8 Hz, 1H), 3.80 (s, 3H), 3.25 (d, J = 13.6 Hz, 1H), 2.83 (t, J = 12.6 Hz, 1H), 2.04 (d, J = 12.5 Hz, 2H), 1.79 (s, 2H).	505.96

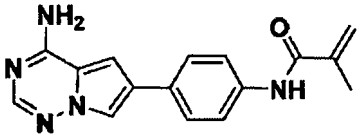
[1132] 实例9

[1133] 流程7



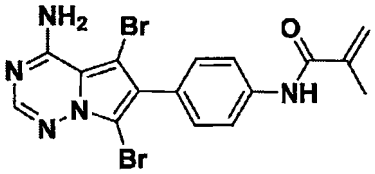
[1134]

[1135] N-(4-(4-氨基吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺

[1136] 

[1137] 步骤1:向可再密封的反应瓶中装入6-溴吡咯并[2,1-f][1,2,4]三嗪-4-胺(500mg,2.34mmol)、2-甲基-N-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]丙-2-烯酰胺(804mg,2.80mmol)、K3PO4(1.48g,7.02mmol)、Pd(dppf)Cl_2(171mg,234μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF/H2O(10mL),且在90℃下搅拌混合物1小时。反应混合物用水(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型TLC(用二氯甲烷/甲醇15:1洗脱)来纯化。真空浓缩,产生呈灰白色无定形固体状的N-(4-{4-氨基吡咯并[2,1-f][1,2,4]三嗪-6-基}苯基)-2-甲基丙-2-烯酰胺(280mg,34%)。

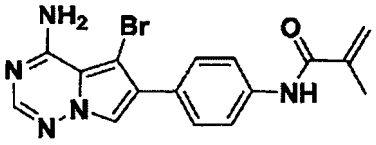
[1138] N-(4-{4-氨基-5,7-二溴吡咯并[2,1-f][1,2,4]三嗪-6-基}苯基)-2-甲基丙-2-烯酰胺

[1139] 

[1140] 步骤2:向圆底烧瓶中装入N-(4-{4-氨基吡咯并[2,1-f][1,2,4]三嗪-6-基}苯基)-2-甲基丙-2-烯酰胺(260mg,886μmol),添加二甲基甲酰胺(5mL),然后在0℃下添加NBS(313mg,1.77mmol),且在0℃下搅拌溶液1小时。反应混合物用Na2SO3(水溶液)(10mL)稀释,且水相用二氯甲烷(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空

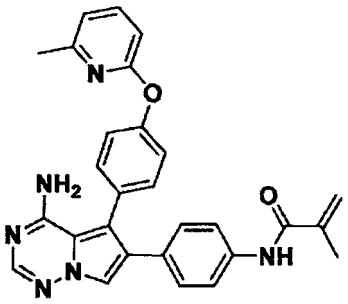
浓缩。所得粗物质通过制备型TLC(用二氯甲烷/甲醇20:1洗脱)来纯化。真空浓缩,产生呈橙色无定形固体状的N-(4-{4-氨基-5,7-二溴吡咯并[2,1-f][1,2,4]三嗪-6-基}苯基)-2-甲基丙-2-烯酰胺(350mg,87%)。

[1141] N-(4-(4-氨基-5-溴吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺

[1142] 

[1143] 步骤3:向可再密封的反应瓶中装入N-(4-{4-氨基-5,7-二溴吡咯并[2,1-f][1,2,4]三嗪-6-基}苯基)-2-甲基丙-2-烯酰胺(300mg,665μmol),添加四氢呋喃(6mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在-78℃下添加n-BuLi(0-8mL,2mmol),且在-78℃下搅拌混合物5分钟。反应混合物用水(5mL)稀释,且水相用二氯甲烷(5mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过TLC(用二氯甲烷/甲醇15:1洗脱)来纯化。真空浓缩,产生呈灰白色无定形固体状的N-(4-{4-氨基-5-溴吡咯并[2,1-f][1,2,4]三嗪-6-基}苯基)-2-甲基丙-2-烯酰胺(100mg,40%)。

[1144] N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺

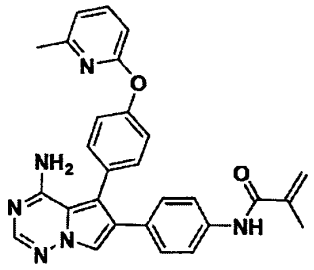
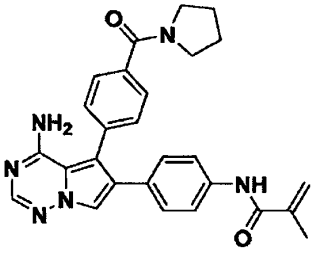
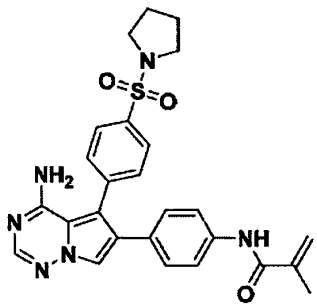
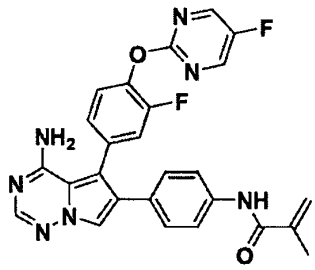
[1145] 

[1146] 步骤4:向可再密封的反应瓶中装入N-(4-{4-氨基-5-溴吡咯并[2,1-f][1,2,4]三嗪-6-基}苯基)-2-甲基丙-2-烯酰胺(90.0mg,241μmol)、2-甲基-6-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]吡啶(82.4mg,265μmol)、K_3PO_4(153mg,722μmol)、Pd(dppf)Cl_2(17.6mg,24.1μmol),添加DMF/H_2O(4mL)及搅拌棒,随后抽真空且用氮气吹扫三次,且在90℃下搅拌混合物1小时。反应混合物用水(10mL)稀释,且水相用二氯甲烷(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(柱:XBridge制备型OBD C18柱,30×150mm 5um;移动相A:未定义,移动相B:未定义;流量:60mL/min;梯度:35B至50B,历时8分钟;220nm;RT1:7.54;RT2:;注射体积:ml;操作次数:;)。冻干产生呈灰白色无定形固体状的N-[4-(4-氨基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基]-2-甲基丙-2-烯酰胺(7.62mg,6%)。

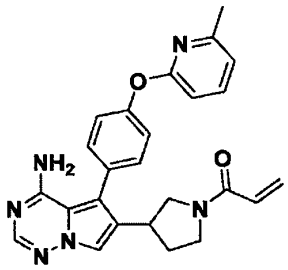
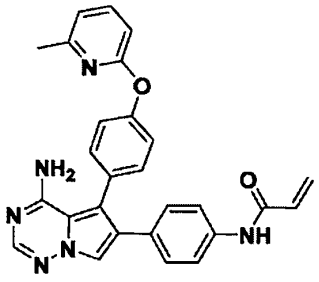
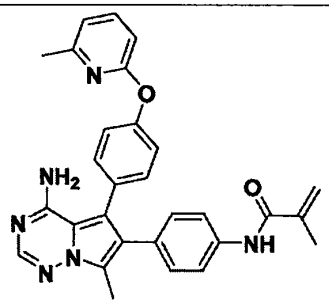
[1147] 根据实例9的方法制备的其它化合物描绘于下表8中。

[1148] 表8.其它示例性化合物

[1149]

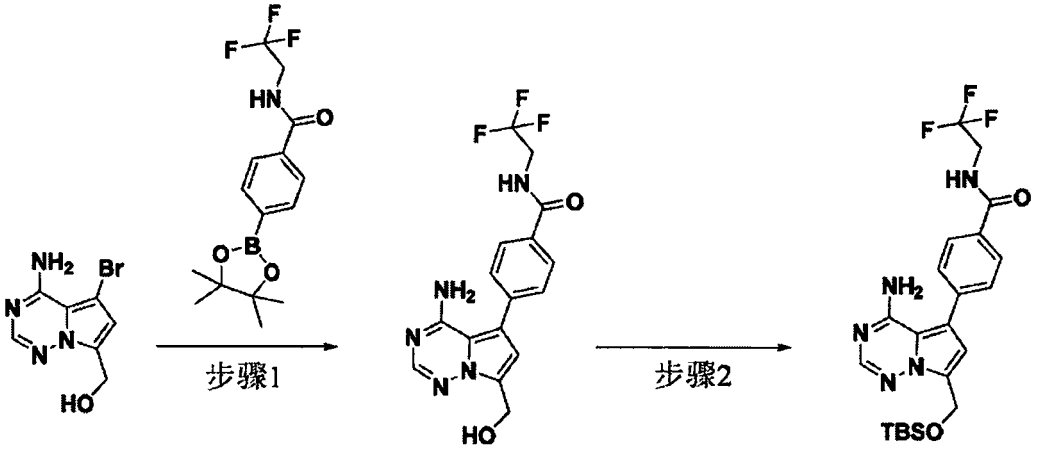
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.03 (s, 1H), 7.90 (s, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.60 - 7.53 (m, 2H), 7.41 - 7.34 (m, 2H), 7.23 - 7.13 (m, 4H), 7.05 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 5.77 (s, 1H), 5.50 (s, 1H), 2.38 (s, 3H), 1.94 (s, 3H).	477.20
N-(4-(4-氨基-5-(4-(吡咯烷-1-羰基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.03 (s, 1H), 7.91 (s, 1H), 7.64 - 7.51 (m, 4H), 7.42 - 7.36 (m, 2H), 7.14 - 7.08 (m, 2H), 5.77 (d, J = 1.3 Hz, 1H), 5.50 (t, J = 1.5 Hz, 1H), 3.48 (dt, J = 13.3, 6.3 Hz, 4H), 2.01 - 1.71 (m, 7H).	467.35
N-(4-(4-氨基-5-(4-(吡咯烷-1-基磺酰基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.04 (s, 1H), 7.94 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.54 (dd, J = 8.4, 5.8 Hz, 4H), 7.01 (d, J = 8.6 Hz, 2H), 5.76 (s, 1H), 5.50 (s, 1H), 3.25 - 3.13 (m, 4H), 1.96 - 1.89 (m, 3H), 1.77 - 1.57 (m, 4H).	503.35
N-(4-(4-氨基-5-(3-氟-4-((5-氟嘧啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 9.77 (s, 1H), 8.81 (s, 2H), 8.02 (s, 1H), 7.93 (s, 1H), 7.62 - 7.56 (m, 2H), 7.49 (t, J = 8.3 Hz, 1H), 7.36 (dd, J = 11.2, 2.0 Hz, 1H), 7.24 (dd, J = 8.3, 2.1 Hz, 1H), 7.21 - 7.10 (m, 2H), 5.79 (s, 1H), 5.54 - 5.45 (m, 1H), 1.95 (t, J = 1.3 Hz, 3H).	500.30

[1150]

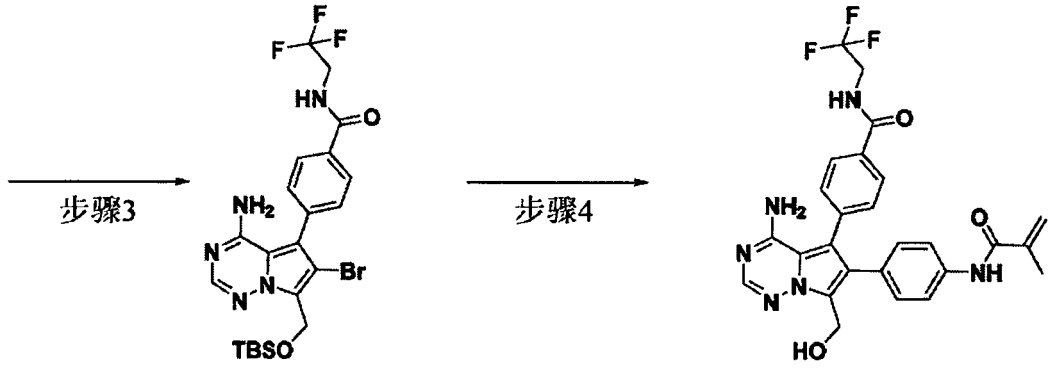
化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 7.86 (d, J = 1.5 Hz, 1H), 7.84 - 7.72 (m, 2H), 7.45 (dd, J = 8.6, 2.6 Hz, 2H), 7.29 - 7.19 (m, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.55 (ddd, J = 16.8, 13.5, 10.3 Hz, 1H), 6.12 (dt, J = 16.9, 2.0 Hz, 1H), 5.65 (ddd, J = 9.8, 6.9, 2.4 Hz, 1H), 4.70 (d, J = 8.6 Hz, 1H), 3.91 - 3.59 (m, 2H), 3.59 - 3.42 (m, 1H), 3.37 (s, 1H), 3.28 - 3.14 (m, 2H), 2.37 (d, J = 3.0 Hz, 3H), 2.25 - 1.85 (m, 2H).	441.30
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 10.12 (s, 1H), 8.03 (s, 1H), 7.90 (s, 1H), 7.81 - 7.73 (m, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.44 - 7.32 (m, 2H), 7.24 - 7.13 (m, 4H), 7.05 (d, J = 7.4 Hz, 1H), 6.84 (s, 1H), 6.42 (dd, J = 16.9, 10.1 Hz, 1H), 6.24 (dd, J = 17.0, 2.0 Hz, 1H), 5.75 (dd, J = 10.1, 2.1 Hz, 1H), 2.38 (s, 3H).	463.30
N-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.96 (s, 1H), 7.83 - 7.71 (m, 1H), 7.64 - 7.57 (m, 2H), 7.35 - 7.24 (m, 2H), 7.16 - 7.06 (m, 4H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 5.77 (t, *J* = 1.1 Hz, 1H), 5.60 - 5.39 (m, 1H), 2.46 (s, 3H), 2.35 (s, 3H), 1.94 (d, *J* = 1.2 Hz, 3H).	491.30

[1151] 实例10

[1152] 流程8.



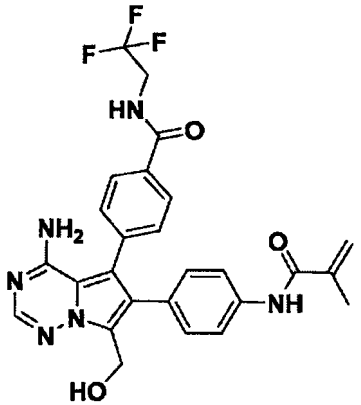
[1153] 1 2 3



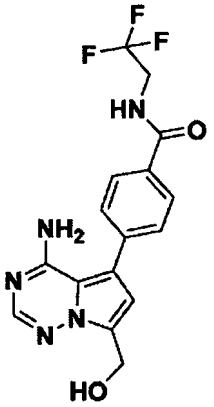
4

[1154] 4-(4-氨基-7-(羟基甲基)-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺

[1155]

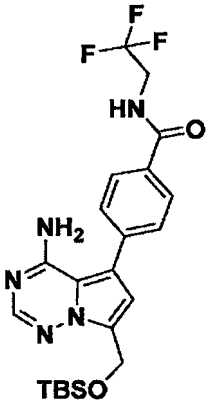


[1156] 4-(4-氨基-7-(羟基甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺

[1157] 

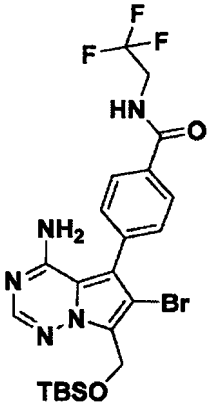
[1158] 步骤1:向可再密封的反应瓶中装入(4-氨基-5-溴吡咯并[2,1-f][1,2,4]三嗪-7-基)甲醇(600mg,2.49mmol)、4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-N-(2,2,2-三氟乙基)苯甲酰胺(983mg,2.99mmol)、Pd(dtbpf)Cl_2(162mg,249μmol)、CsF(1.14g,7.47mmol)、DMF:水=16:1(8mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取。分离有机相且经Na_2SO_4干燥,过滤且真空浓缩。所得粗物质通过制备型TLC纯化。真空浓缩,产生呈黄色油状的4-(4-氨基-7-(羟基甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺(400mg,44%)。

[1159] 4-(4-氨基-7-(((叔丁基二甲基硅烷基)氧基)甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺

[1160] 

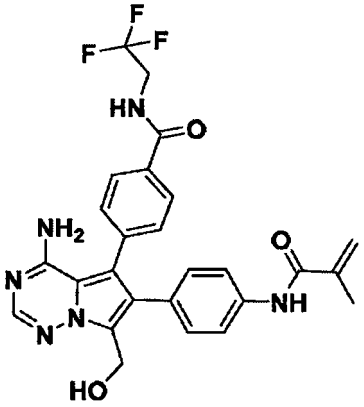
[1161] 步骤2:向可再密封的反应瓶中装入4-(4-氨基-7-(羟基甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺(380mg,1.04mmol)、咪唑(283mg,4.16mmol)、DMF(5mL)及搅拌棒。添加TBSCl(314mg,2.08mmol),且在室温下搅拌溶液1小时。所得混合物经由C18柱纯化。真空浓缩,产生呈黄色无定形固体状的4-(4-氨基-7-(((叔丁基二甲基硅烷基)氧基)甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺(420mg,84%)。

[1162] 4-(4-氨基-6-溴-7-(((叔丁基二甲基硅烷基)氧基)甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺

[1163] 

[1164] 步骤3:向圆底烧瓶中装入4-(4-氨基-7-(((叔丁基二甲基硅烷基)氧基)甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺(400mg,0.84mmol)、二甲基甲酰胺(5mL)及搅拌棒。添加NBS(225mg,1.00mmol),且在室温下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取。分离有机相且经Na_2SO_4干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色无定形固体状的4-(4-氨基-6-溴-7-(((叔丁基二甲基硅烷基)氧基)甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺(450mg,94%)。

[1165] 6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺

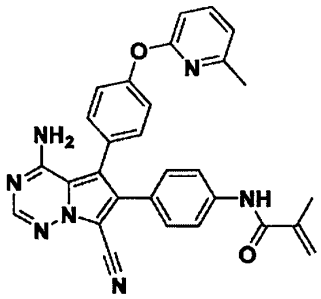
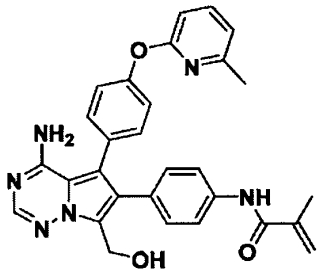
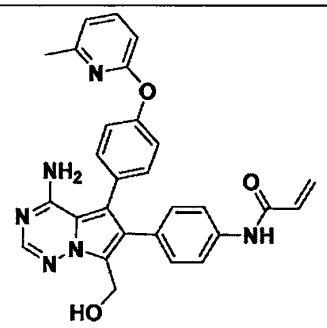
[1166] 

[1167] 步骤4:向可再密封的反应瓶中装入4-(4-氨基-6-溴-7-(((叔丁基二甲基硅烷基)氧基)甲基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺(200mg,0.36mmol)、N-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)甲基丙烯酰胺(124mg,0.43mmol)、Pd(dtbpf)Cl_2(23.4mg,36μmol)、CsF(164mg,1.08mmol)、DMF:水=16:1(4mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下、在N_2下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取。收集有机相且经Na_2SO_4干燥,过滤且真空浓缩。所得粗物质通过制备型HPLC纯化(柱:XBridge制备型OBD C18柱,19*250mm,5um;移动相A:水(10MMOL/L NH_4HCO_3),移动相B:ACN;流量:25mL/min;梯度:20B至50B,历时8分钟;220nm;RT1:7.23;)。冻干产生呈灰白色无定形固体状的4-(4-氨基-7-(羟基甲基)-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺(30.4mg,16%)。

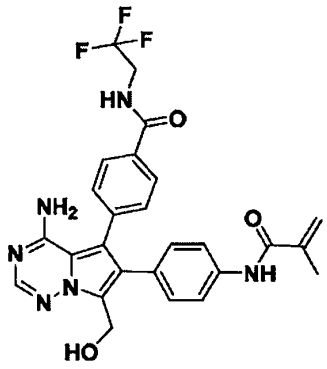
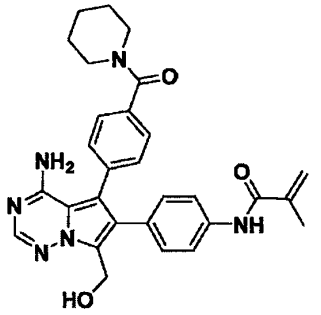
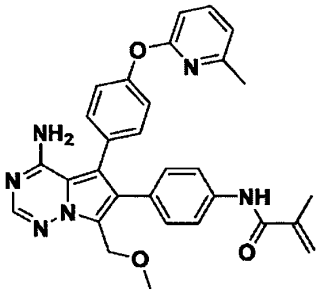
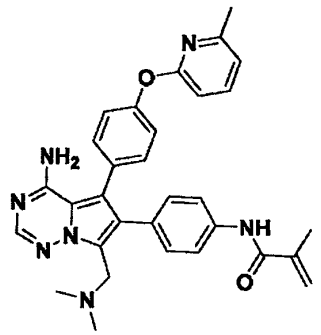
[1168] 根据实例10的方法制备的其它化合物描绘于下表9中。

[1169] 表9.其它示例性化合物

[1170]

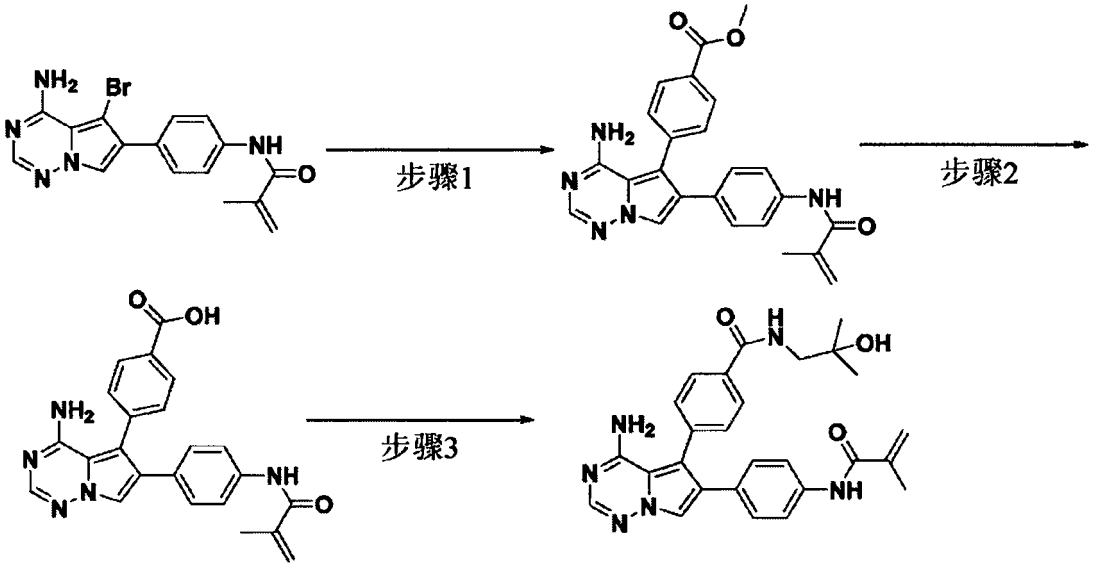
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-氰基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.46 (s, 1H), 8.20 (s, 1H), 7.80 - 7.63 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 7.25 - 7.14 (m, 4H), 7.04 (d, J = 7.3 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.79 (s, 1H), 5.53 (s, 1H), 2.36 (s, 3H), 1.94 (s, 3H).	502.35
N-(4-(4-氨基-7-(羟基甲基)-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.99 (s, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.64 - 7.55 (m, 2H), 7.32 - 7.26 (m, 2H), 7.22 - 7.10 (m, 4H), 7.03 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 5.77 (s, 1H), 5.51 (s, 1H), 5.17 (t, J = 5.0 Hz, 1H), 4.69 (d, J = 4.9 Hz, 2H), 2.36 (s, 3H), 1.94 (s, 3H).	507.35
N-(4-(4-氨基-7-(羟基甲基)-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.99 (s, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.63 - 7.56 (m, 2H), 7.33 - 7.25 (m, 2H), 7.24 - 7.17 (m, 2H), 7.17 - 7.09 (m, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.43 (dd, J = 17.0, 10.1 Hz, 1H), 6.25 (dd, J = 17.0, 2.1 Hz, 1H), 5.75 (dd, J = 10.1, 2.1 Hz, 1H), 5.16 (t, J = 5.0 Hz, 1H), 4.69 (d, J = 5.0 Hz, 2H), 2.36 (s, 3H).	493.35

[1171]

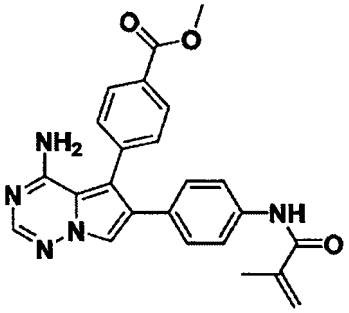
化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-7-(羟基甲基)-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.76 (s, 1H), 9.13 (s, 1H), 8.01 (s, 1H), 7.93 - 7.83 (m, 2H), 7.61 - 7.54 (m, 2H), 7.43 - 7.30 (m, 2H), 7.18 - 7.08 (m, 2H), 5.77 (d, J = 1.2 Hz, 1H), 5.51 (s, 0H), 5.16 (t, J = 4.9 Hz, 1H), 4.68 (d, J = 5.0 Hz, 2H), 4.19 - 4.00 (m, 2H), 1.93 (t, J = 1.2 Hz, 3H).	525
N-(4-(4-氨基-7-(羟基甲基)-5-(4-(哌啶-1-羰基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 7.99 (s, 1H), 7.60 - 7.53 (m, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.32 - 7.26 (m, 2H), 7.15 - 7.09 (m, 2H), 5.77 (s, 1H), 5.50 (d, J = 1.9 Hz, 1H), 5.17 (s, 1H), 4.68 (s, 2H), 3.57-3.35 (d, J = 2.8 Hz, 4H), 1.93 (t, J = 1.2 Hz, 3H), 1.69 - 1.40 (m, 6H).	511.40
N-(4-(4-氨基-7-(甲氧基甲基)-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.00 (s, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.36 - 7.25 (m, 2H), 7.12 (d, J = 8.3 Hz, 4H), 7.03 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 5.77 (s, 1H), 5.50 (s, 1H), 4.60 (s, 2H), 3.31 (s, 3H), 2.35 (s, 3H), 1.94 (d, J = 1.3 Hz, 3H).	521.40
N-(4-(4-氨基-7-((二甲基氨基)甲基)-5-(4-((6-甲基吡啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.96 (s, 1H), 7.79 - 7.70 (m, 1H), 7.62 - 7.56 (m, 2H), 7.34 - 7.26 (m, 2H), 7.26 - 7.20 (m, 2H), 7.15 - 7.07 (m, 2H), 7.03 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 5.77 (s, 1H), 5.50 (t, J = 1.5 Hz, 1H), 3.71 (s, 2H), 2.36 (s, 3H), 2.11 (s, 6H), 1.94 (d, J = 1.2 Hz, 3H).	534.35

[1172] 实例11

[1173] 流程9

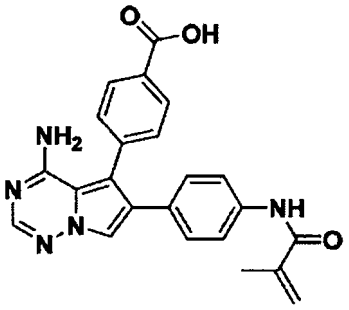
[1174] 

[1175] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7H-环戊并[d]嘧啶-5-基)苯甲酸甲酯

[1176] 

[1177] 步骤1:向圆底烧瓶中装入N-(4-{4-氨基-5-溴-7H-环戊并[d]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺(800mg,2.15mmol)、4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯甲酸甲酯(731mg,2.79mmol)、Pd(dtbpf)Cl2(139mg,215μmol)、CsF(980mg,6.45mmol)、DMF:H_2O=16:1(8mL)及搅拌棒。在90℃下、在N_2下搅拌溶液2小时。反应混合物用水(50mL)稀释且用EtOAc(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈灰白色无定形固体状的4-{4-氨基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-环戊并[d]嘧啶-5-基}苯甲酸甲酯(600mg,56%)。

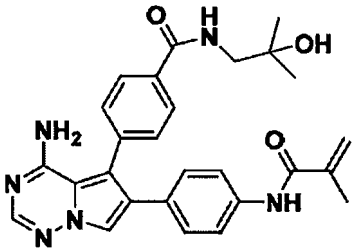
[1178] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7H-环戊并[d]嘧啶-5-基)苯甲酸

[1179] 

[1180] 步骤2:向圆底烧瓶中装入4-{4-氨基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-环戊并[d]嘧啶-5-基}苯甲酸甲酯(580mg,1.35mmol)、THF:LiOH(2M)=1:1(6mL)及搅拌棒。在室温下搅拌溶液3小时。溶液pH值用HCl水溶液调节至6~7。通过添加HCl而使产物沉淀且干

燥。此产生呈灰白色无定形固体状的4-{4-氨基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7H-环戊并[d]嘧啶-5-基}苯甲酸(350mg,63%)。

[1181] 4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2-羟基-2-甲基丙基)苯甲酰胺

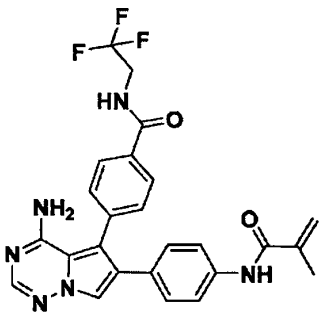
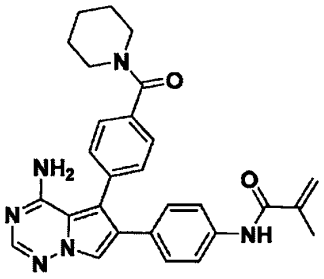
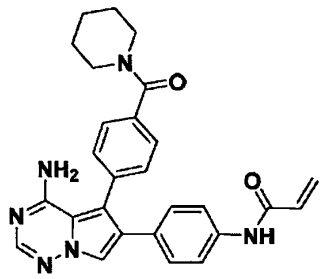
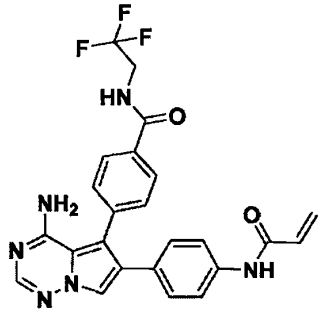
[1182] 

[1183] 步骤3:向可再密封的反应瓶中装入4-{4-氨基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]-7aH-环戊并[d]嘧啶-5-基}苯甲酸(60mg,145μmol)、1-氨基-2-甲基丙-2-醇(15.5mg,174μmol)、HATU(55.2mg,145μmol)、DIEA(37.4mg,290μmol)、二甲基甲酰胺(10mL)及搅拌棒。在室温下搅拌混合物1小时。反应混合物用水淬灭且通过HPLC纯化(柱:XBridge制备型C18 OBD柱,5um,19*150mm;移动相A:水(10MMOL/LNH_4HCO_3),移动相B:ACN;流量:25mL/min;梯度:15B至50B,历时7分钟;254/220nm;RT1:7.58;)。冻干产生呈白色无定形固体状的4-{4-氨基-6-[4-(2-甲基丙-2-烯酰胺基)苯基]吡咯并[2,1-f][1,2,4]三嗪-5-基}-N-(2-羟基-2-甲基丙基)苯甲酰胺(40.2mg,56.4%)。

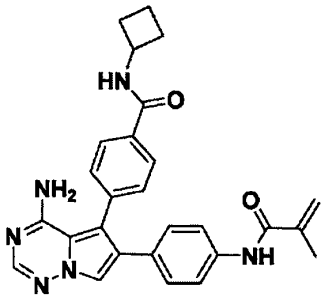
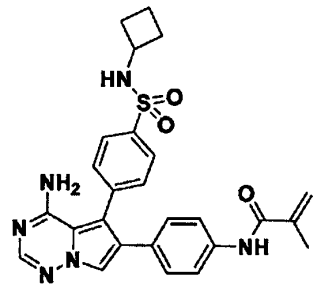
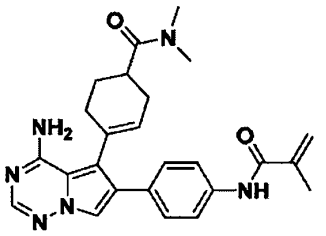
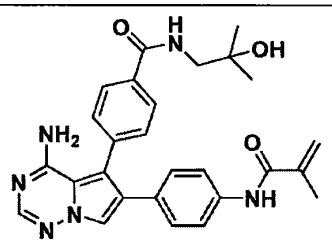
[1184] 根据实例11的方法制备的其它化合物描绘于下表10中。

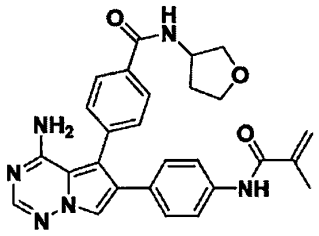
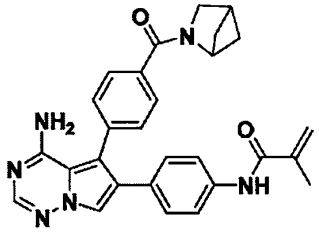
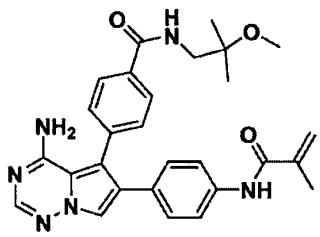
[1185] 表10.其它示例性化合物

[1186]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 9.18 (t, J = 6.3 Hz, 1H), 8.03 (s, 1H), 8.00 - 7.89 (m, 3H), 7.59 - 7.51 (m, 2H), 7.51 - 7.37 (m, 2H), 7.14 - 7.03 (m, 2H), 5.77 (d, J = 1.1 Hz, 1H), 5.50 (t, J = 1.5 Hz, 1H), 4.12 (qd, J = 9.7, 6.1 Hz, 2H), 1.93 (t, J = 1.2 Hz, 3H).	485.25
N-(4-(4-氨基-5-(4-(哌啶-1-羰基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.63 - 7.50 (m, 2H), 7.50 - 7.28 (m, 4H), 7.17 - 7.03 (m, 2H), 5.77 (s, 1H), 5.57 - 5.46 (m, 1H), 3.48 (d, J = 89.5 Hz, 4H), 1.75 - 1.37 (m, 6H).	481.40
N-(4-(4-氨基-5-(4-(哌啶-1-羰基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.11 (s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.55 - 7.48 (m, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.14 - 7.03 (m, 2H), 6.56 - 6.35 (m, 1H), 6.24 (dd, J = 17.0, 2.1 Hz, 1H), 5.74 (dd, J = 10.1, 2.1 Hz, 1H), 3.59 (s, 4H), 1.64 (s, 2H), 1.54 (s, 4H).	467.35
4-(6-(4-丙烯酰胺基苯基)-4-氨基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2,2,2-三氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.11 (s, 1H), 9.18 (t, J = 6.3 Hz, 1H), 8.03 (s, 1H), 8.01 - 7.89 (m, 3H), 7.56 - 7.50 (m, 2H), 7.50 - 7.33 (m, 2H), 7.17 - 7.05 (m, 2H), 6.41 (dd, J = 17.0, 10.1 Hz, 1H), 6.24 (dd, J = 17.0, 2.1 Hz, 1H), 5.74 (dd, J = 10.0, 2.1 Hz, 1H), 4.21 - 4.03 (m, 2H).	481.30

[1187]

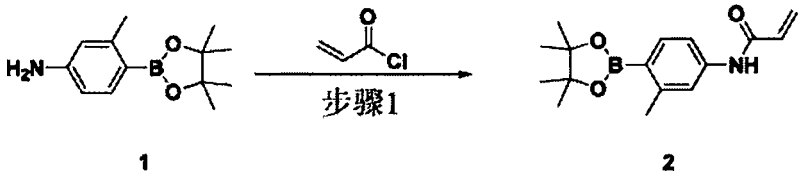
化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-环丁基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.75 (s, 1H), 8.70 (d, J = 7.4 Hz, 1H), 8.03 (s, 1H), 7.91 (d, J = 8.3 Hz, 3H), 7.53 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 5.76 (s, 1H), 5.50 (s, 1H), 4.53 - 4.26 (m, 1H), 2.22 (s, 2H), 2.09 (t, J = 10.6 Hz, 2H), 1.93 (s, 3H), 1.68 (s, 2H).	467.35
N-(4-(4-氨基-5-(4-(N-环丁基胺磺酰基)苯基)吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.75 (s, 1H), 8.04 (s, 1H), 7.98 (s, 1H), 7.93 (s, 1H), 7.87 - 7.80 (m, 2H), 7.55 - 7.49 (m, 4H), 7.08 - 7.01 (m, 2H), 5.75 (s, 1H), 5.50 (t, *J* = 1.5 Hz, 1H), 3.68 (s, 1H), 2.02 - 1.85 (m, 5H), 1.79 - 1.65 (m, 2H), 1.63 - 1.38 (m, 2H).	503.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N,N-二甲基环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.82 (s, 1H), 7.90 (s, 1H), 7.78 (s, 1H), 7.75 - 7.66 (m, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.25 (s, 1H), 5.90 (d, J = 4.4 Hz, 1H), 5.81 (t, J = 1.1 Hz, 1H), 5.52 (t, J = 1.5 Hz, 1H), 3.20 (d, J = 13.7 Hz, 1H), 3.06 (s, 3H), 2.85 (s, 3H), 2.36 (s, 2H), 1.97 (t, J = 1.2 Hz, 3H), 1.90 (s, 2H), 1.77 (s, 1H).	445.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2-羟基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.74 (s, 1H), 8.34 (t, J = 6.2 Hz, 1H), 8.03 (s, 1H), 7.93 (d, J = 8.5 Hz, 3H), 7.56 - 7.48 (m, 2H), 7.45 - 7.39 (m, 2H), 7.18 - 7.06 (m, 2H), 5.76 (d, J = 1.4 Hz, 1H), 5.53 - 5.43 (m, 1H), 4.56 (s, 1H), 3.28 (d, J = 6.1 Hz, 2H), 1.92 (t, J = 1.2 Hz, 3H), 1.12 (s, 6H).	485.35

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(四氢呋喃-3-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.62 (d, J = 6.4 Hz, 1H), 8.03 (s, 1H), 7.93 (d, J = 8.0 Hz, 3H), 7.62 - 7.49 (m, 2H), 7.46 - 7.39 (m, 2H), 7.14 - 7.04 (m, 2H), 5.76 (s, 1H), 5.49 (t, J = 1.5 Hz, 1H), 4.51 - 4.41 (m, 1H), 3.87 (dd, J = 9.0, 6.6 Hz, 2H), 3.73 (td, J = 8.1, 5.7 Hz, 1H), 3.61 (dd, J = 8.9, 4.4 Hz, 1H), 2.16 (dq, J = 12.6, 7.6 Hz, 1H), 1.99 - 1.81 (m, 4H).	483.15
N-(4-(5-(4-(2-氮杂双环[2.1.1]己烷-2-羰基)苯基)-4-氨基吡咯并[2,1-f][1,2,4]三嗪-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.57 - 7.47 (m, 3H), 7.39 (d, J = 7.3 Hz, 2H), 7.17 - 7.06 (m, 2H), 5.77 (d, J = 1.5 Hz, 1H), 5.49 (t, J = 1.5 Hz, 1H), 4.55 (dd, J = 147.8, 7.0 Hz, 1H), 3.48 (d, J = 10.6 Hz, 2H), 2.91 (d, J = 16.9 Hz, 1H), 2.05 - 1.84 (m, 5H), 1.51 (s, 1H), 1.37 (s, 1H).	479.35
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-(2-甲氧基-2-甲基丙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.33 (t, *J* = 6.2 Hz, 1H), 8.03 (s, 1H), 7.95 - 7.88 (m, 3H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 1.9 Hz, 2H), 7.15 - 7.06 (m, 2H), 5.76 (s, 1H), 5.49 (s, 1H), 3.35 (d, *J* = 6.2 Hz, 2H), 3.16 (s, 3H), 1.92 (t, *J* = 1.2 Hz, 3H), 1.13 (s, 6H).	499.25

[1188]

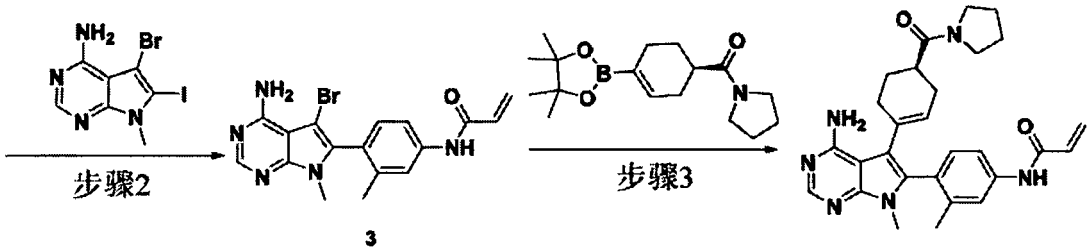
[1189] 实例12

[1190] 流程10



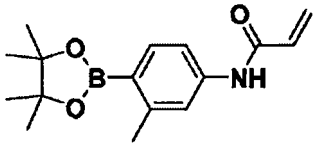
1 2

[1191]



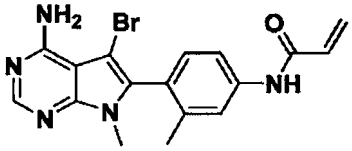
3

[1192] N-(3-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)丙烯酰胺

[1193] 

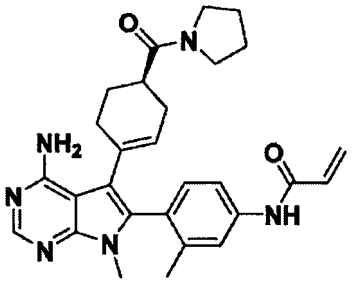
[1194] 步骤1:向圆底烧瓶中装入3-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯胺(10g,42.8mmol)、丙-2-烯酰氯(3.87g,42.8mmol)、吡啶(10.1g,128mmol)、二氯甲烷(150mL)及搅拌棒。在0℃下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取。有机相经Na_2SO_4干燥,过滤且真空蒸发。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色油状的N-(3-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)丙烯酰胺(12g,98%)。

[1195] N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺

[1196] 

[1197] 步骤2:向圆底烧瓶中装入N-[3-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]丙-2-烯酰胺(1g,3.48mmol)、5-溴-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(1.22g,3.48mmol)、Pd(dppf)Cl_2(254mg,348μmol)、K_3PO_4(2.20g,10.4mmol)、DMF/H_2O(16:1)(15mL)及搅拌棒。在50℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,过滤且真空蒸发。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈灰白色无定形固体状的N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺(440mg,33%)。

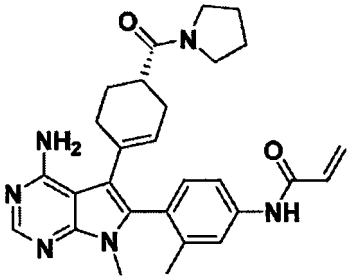
[1198] (R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺

[1199] 

[1200] 步骤3:向可再密封的反应瓶中装入N-(4-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3-甲基苯基)丙-2-烯酰胺(200mg,517μmol)、1-[(1R)-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)环己-3-烯-1-羰基]吡咯烷(156mg,517μmol)、Pd(pddf)Cl_2(37.8mg,517μmol)、Na_2CO_3(164mg,1.55mmol)、DMF(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物2小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,过滤且真空蒸发。所得粗物质通过制备型HPLC纯化(柱:YMC-Actus Triart C18,30*250,5um;移动相A:水(10MMOL/L NH_4HCO_3),移动相B:ACN;流量:50mL/min;梯度:40B至62B,历时8分钟;220nm;RT1:6.83)。冻干产生呈灰白色无定形固体状的(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-

基)-3-甲基苯基)丙烯酰胺(40mg,16%)。

[1201] (S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺

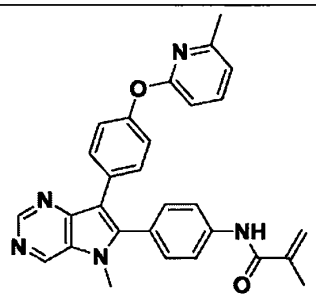
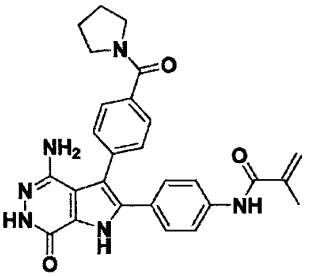
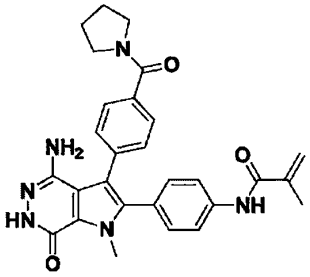
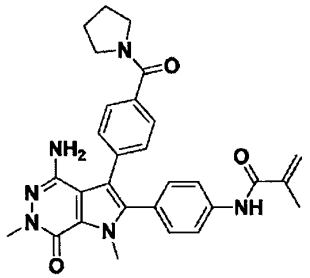
[1202] 

[1203] 步骤4:向可再密封的反应瓶中装入N-(4-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3-甲基苯基)丙-2-烯酰胺(240mg,621μmol)、Pd(dppf)Cl_2(45.4mg,62.1μmol)、Na_2CO_3(197mg,1.86mmol)、1-[(1S)-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)环己-3-烯-1-羰基]吡咯烷(189240mg,621μmol)、二甲基甲酰胺/H_2O(8mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物2小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,过滤且真空蒸发。所得粗物质通过制备型HPLC纯化(柱:YMC-Actus Triart C18,30*250,5um;移动相A:水(10MMOL/L NH_4HCO_3),移动相B:ACN;流量:50mL/min;梯度:40B至60B,历时8分钟;220nm;RT1:7.67;RT2:;注射体积:ml;操作次数:;)。冻干产生呈灰白色无定形固体状的(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺(39mg,14%)。

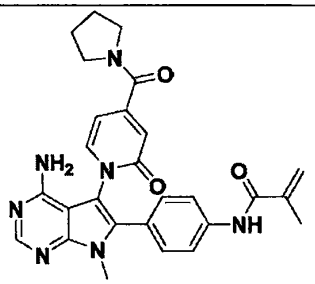
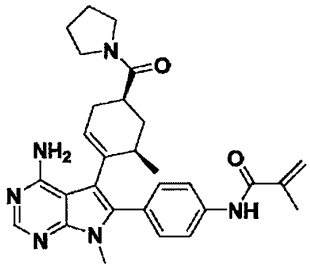
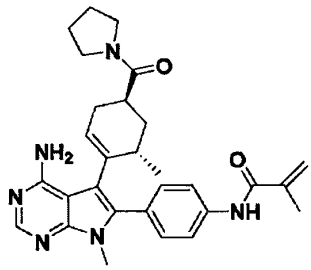
[1204] 根据实例12的方法制备的其它化合物描绘于下表11中。

[1205] 表11.其它示例性化合物

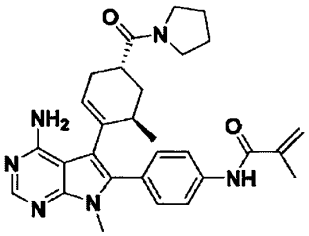
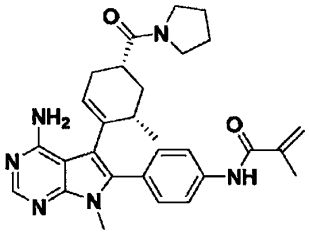
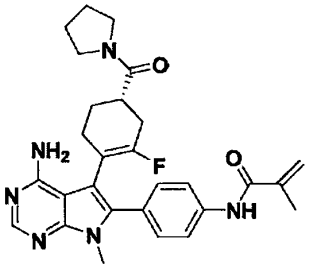
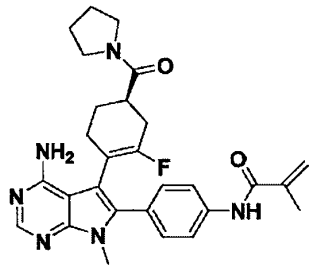
[1206]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-甲基-7-(4-((6-甲基吡啶-2-基)氧基)苯基)-5H-吡咯并[3,2-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.16 (s, 1H), 8.94 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.72 (t, J = 7.8 Hz, 1H), 7.48 (dd, J = 20.9, 8.5 Hz, 4H), 7.08 - 6.96 (m, 3H), 6.75 (d, J = 8.2 Hz, 1H), 5.85 (s, 1H), 5.57 (s, 1H), 3.75 (s, 3H), 2.34 (s, 3H), 1.98 (s, 3H).	476.15
N-(4-(4-氨基-7-侧氧基-3-(4-(吡咯烷-1-羰基)苯基)-6,7-二氢-1H-吡咯并[2,3-d]哒嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 11.38 (s, 1H), 9.83 (s, 1H), 7.62 - 7.54 (m, 4H), 7.45 - 7.35 (m, 2H), 7.28 - 7.21 (m, 2H), 5.78 (s, 1H), 5.52 (s, 1H), 4.55 (s, 2H), 3.46 (dt, J = 23.1, 6.3 Hz, 4H), 1.98 - 1.80 (m, 7H).	483.25
N-(4-(4-氨基-1-甲基-7-侧氧基-3-(4-(吡咯烷-1-羰基)苯基)-6,7-二氢-1H-吡咯并[2,3-d]哒嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H), 9.91 (s, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 7.7 Hz, 2H), 7.26 (dd, J = 12.9, 8.1 Hz, 4H), 5.79 (s, 1H), 5.53 (s, 1H), 4.59 (s, 2H), 3.98 (s, 3H), 3.45 (t, J = 7.0 Hz, 2H), 1.93 (s, 3H), 1.82 (dt, J = 18.4, 7.0 Hz, 4H).	497.35
N-(4-(4-氨基-1,6-二甲基-7-侧氧基-3-(4-(吡咯烷-1-羰基)苯基)-6,7-二氢-1H-吡咯并[2,3-d]哒嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.73 - 7.66 (m, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.31 - 7.21 (m, 4H), 5.79 (s, 1H), 5.53 (s, 1H), 4.72 (s, 2H), 3.98 (s, 3H), 3.55 (s, 3H), 3.45 (t, J = 6.8 Hz, 2H), 3.37 (t, J = 6.4 Hz, 2H), 1.94 (s, 3H), 1.84 (m, J = 18.4 Hz, 4H).	511.25

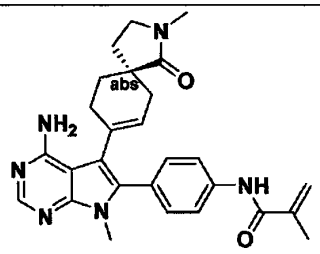
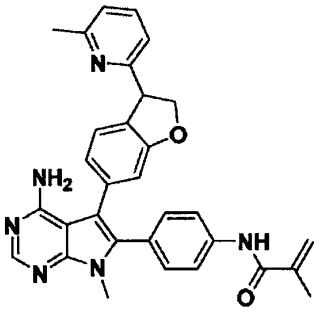
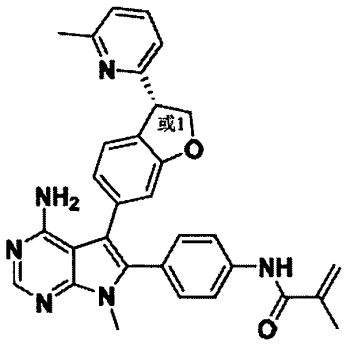
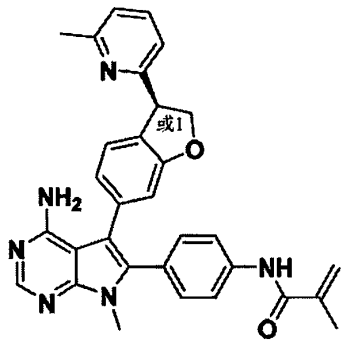
[1207]

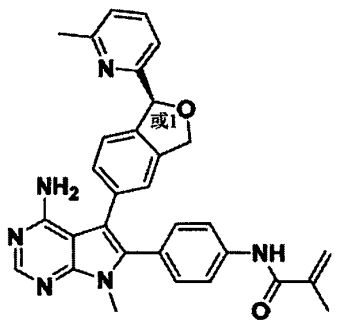
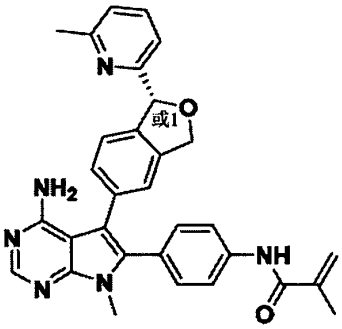
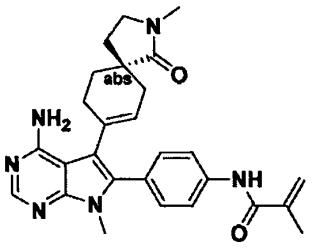
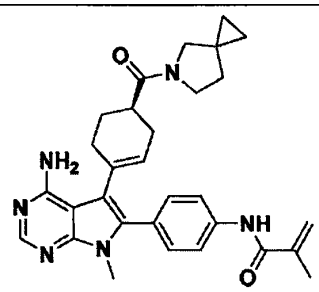
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(2-侧氧基-4-(吡咯烷-1-羰基)吡啶-1(2H)-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.21 (s, 1H), 7.84 - 7.71 (m, 2H), 7.44 (d, J = 7.0 Hz, 1H), 7.36 - 7.25 (m, 2H), 6.49 (d, J = 1.7 Hz, 1H), 6.32 (s, 2H), 6.14 (dd, J = 7.0, 1.8 Hz, 1H), 5.88 - 5.79 (m, 1H), 5.54 (d, J = 1.8 Hz, 1H), 3.65 (s, 3H), 3.40 (td, J = 11.7, 11.3, 5.5 Hz, 3H), 1.95 (d, J = 1.2 Hz, 3H), 1.89 - 1.80 (m, 4H).	498.25
(R)-N-(4-(4-氨基-7-甲基-5-(2-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) 8.15 (s, 1H), 7.82 - 7.75 (m, 2H), 7.46 (d, J = 8.3 Hz, 2H), 5.97 (s, 1H), 5.85 (t, J = 1.0 Hz, 1H), 5.59 - 5.53 (m, 1H), 3.67 (s, 4H), 3.60 - 3.45 (m, 1H), 3.49 - 3.35 (m, 2H), 2.98 (s, 1H), 2.46 (d, J = 9.9 Hz, 1H), 2.37 (s, 1H), 2.07 (t, J = 1.2 Hz, 3H), 2.01 - 1.90 (m, 5H), 1.72 (s, 1H), 1.55 (d, J = 12.8 Hz, 1H), 0.90 (s, 3H).	499.25
(R)-N-(4-(4-氨基-7-甲基-5-(2-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, 甲醇-d_4) 8.15 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 5.97 (s, 1H), 5.87 - 5.82 (m, 1H), 5.56 (q, J = 1.6 Hz, 1H), 3.67 (s, 4H), 3.60 - 3.51 (m, 1H), 3.50 - 3.35 (m, 2H), 2.98 (s, 1H), 2.60 - 2.46 (d, J = 10.4 Hz, 1H), 2.37 (s, 1H), 2.07 (t, J = 1.3 Hz, 3H), 2.00 (p, J = 6.5 Hz, 2H), 1.95 - 1.85 (m, 2H), 1.80 - 1.60 (s, 1H),1.59 - 1.50 (m, 1H), 1.1 - 0.45 (m, 3H).	499.25

[1208]

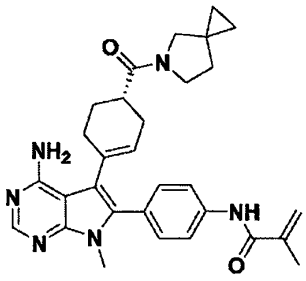
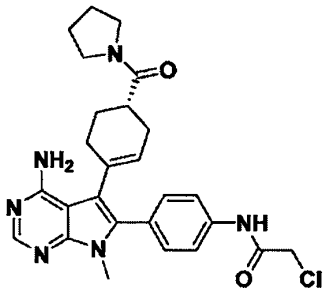
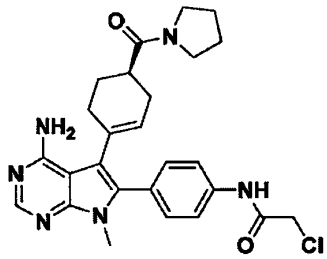
化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(2-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, 甲醇-d_4) 8.15 (s, 1H), 7.83 - 7.75 (m, 2H), 7.52 - 7.45 (m, 2H), 6.03 (t, J = 3.1 Hz, 1H), 5.85 (t, J = 0.9 Hz, 1H), 5.57 (d, J = 1.9 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 1H), 3.62 - 3.49 (m, 1H), 3.48 - 3.35 (m, 2H), 2.75 (s, 1H), 2.49 (s, 1H), 2.37 (s, 1H), 2.07 (t, J = 1.2 Hz, 3H), 1.99 (q, J = 6.6 Hz, 3H), 1.95 - 1.85 (m, 2H), 1.84 (s, 1H), 1.55 (q, J = 11.1 Hz, 1H), 0.74 (d, J = 7.1 Hz, 3H).	499.20
(S)-N-(4-(4-氨基-7-甲基-5-(2-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) 8.15 (s, 1H), 7.83 - 7.75 (m, 2H), 7.51 - 7.45 (m, 2H), 6.06 - 6.00 (m, 1H), 5.85 (t, J = 1.0 Hz, 1H), 5.57 (q, J = 1.8 Hz, 1H), 3.66 (s, 3H), 3.61 - 3.48 (m, 2H), 3.43 - 3.35 (m, 2H), 3.13 - 2.71 (s, 1H), 2.75 (s, 1H), 2.37 (s, 1H), 2.10 - 1.91 (m, 6H), 1.89 (dd, J = 10.4, 4.4 Hz, 2H), 1.84 (s, 1H), 1.62 - 1.49 (m, 1H), 0.74 (d, J = 7.1 Hz, 3H).	499.30
(S)-N-(4-(4-氨基-5-(2-氟-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) 8.15 (d, J = 11.9 Hz, 1H), 7.84 - 7.75 (m, 2H), 7.48 - 7.40 (m, 2H), 5.85 (s, 1H), 5.57 (s, 1H), 3.69 (d, J = 5.4 Hz, 3H), 3.67 - 3.50 (m, 1H), 3.52 - 3.36 (m, 2H), 3.16 (d, J = 1.7 Hz, 2H), 2.48 (t, J = 16.7 Hz, 2H), 2.15 (s, 1H), 2.10 - 1.69 (m, 10H).	503.25
(R)-N-(4-(4-氨基-5-(2-氟-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) 8.16 (d, J = 8.6 Hz, 1H), 7.84 - 7.75 (m, 2H), 7.48 - 7.40 (m, 2H), 5.85 (t, J = 1.0 Hz, 1H), 5.57 (d, J = 2.0 Hz, 1H), 3.69 (d, J = 3.1 Hz, 3H), 3.67 - 3.55 (m, 1H), 3.55 - 3.35 (m, 3H), 3.16 (s, 1H), 2.50 (d, J = 11.2 Hz, 2H), 2.15 (s, 1H), 2.07 (t, J = 1.2 Hz, 3H), 1.99 (p, J = 6.5 Hz, 2H), 1.94 - 1.86 (m, 4H), 1.69 (s, 1H).	503.25

[1209]

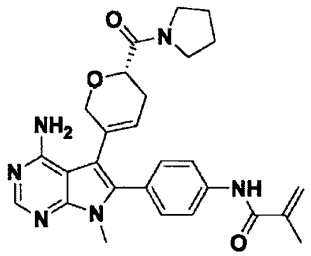
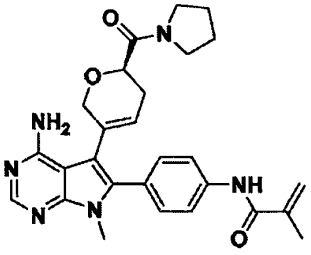
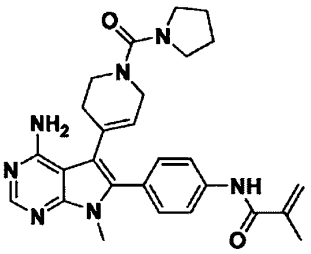
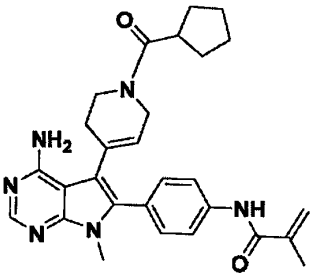
化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-7-甲基-5-(2-甲基-1-侧氧基-2-氮杂螺[4.5]癸-7-烯-8-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.11 (s, 1H), 7.84 - 7.77 (m, 2H), 7.47 - 7.41 (m, 2H), 6.65 (s, 1H), 5.83 (s, 1H), 5.71 (d, J = 4.0 Hz, 1H), 5.56 (d, J = 1.8 Hz, 1H), 3.59 (s, 3H), 3.26 (ddt, J = 9.7, 7.1, 3.4 Hz, 2H), 2.73 (s, 3H), 2.27 (d, J = 17.7 Hz, 1H), 2.17 - 2.01 (m, 2H), 1.97 (s, 3H), 1.90 (s, 1H), 1.87 - 1.72 (m, 3H), 1.45 - 1.31 (m, 1H).	471.25
N-(4-(4-氨基-7-甲基-5-(3-(6-甲基吡啶-2-基)-2,3-二氢苯并呋喃-6-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.18 (s, 1H), 7.77 - 7.64 (m, 3H), 7.34 - 7.24 (m, 2H), 7.21 - 7.12 (m, 2H), 7.06 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 1.5 Hz, 1H), 6.69 (dd, J = 16.4, 1.5 Hz, 1H), 6.25 - 5.61 (m, 2H), 5.61 - 5.50 (m, 1H), 4.97 - 4.68 (m, 3H), 3.58 (s, 3H), 2.45 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	517.25
(R)-N-(4-(4-氨基-7-甲基-5-(3-(6-甲基吡啶-2-基)-2,3-二氢苯并呋喃-6-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.18 (s, 1H), 7.78 - 7.63 (m, 3H), 7.39 - 7.25 (m, 2H), 7.13 (t, J = 7.0 Hz, 2H), 7.06 (d, J = 7.6 Hz, 1H), 6.72 (dd, J = 7.6, 1.5 Hz, 1H), 6.67 (d, J = 1.4 Hz, 1H), 5.80 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 5.00 - 4.69 (m, 3H), 3.58 (s, 3H), 2.45 (s, 3H), 1.95 (d, J = 1.4 Hz, 3H).	517.25
(S)-N-(4-(4-氨基-7-甲基-5-(3-(6-甲基吡啶-2-基)-2,3-二氢苯并呋喃-6-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.18 (s, 1H), 7.79 - 7.61 (m, 3H), 7.33 - 7.27 (m, 2H), 7.13 (t, J = 7.0 Hz, 2H), 7.06 (d, J = 7.6 Hz, 1H), 6.72 (dd, J = 7.6, 1.5 Hz, 1H), 6.67 (d, J = 1.5 Hz, 1H), 5.80 (s, 1H), 5.54 (t, J = 1.6 Hz, 1H), 4.98 - 4.74 (m, 3H), 3.58 (s, 3H), 2.45 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	517.25

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(1-(6-甲基吡啶-2-基)-1,3-二氢异苯并呋喃-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.74 - 7.62 (m, 3H), 7.33 - 7.19 (m, 5H), 7.19 - 7.09 (m, 2H), 6.68 - 5.38 (m, 5H), 5.29 (dd, J = 12.7, 2.8 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 3.59 (s, 3H), 2.50 (s, 3H), 1.94 (d, J = 1.4 Hz, 3H).	517.25
(R)-N-(4-(4-氨基-7-甲基-5-(1-(6-甲基吡啶-2-基)-1,3-二氢异苯并呋喃-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.20 (s, 1H), 7.81 - 7.61 (m, 3H), 7.35 - 7.10 (m, 7H), 6.75 - 5.41 (m, 5H), 5.29 (dd, J = 12.8, 2.8 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 3.59 (s, 3H), 2.50 (s, 3H), 1.94 (s, 3H).	517.30
[1210] (S)-N-(4-(4-氨基-7-甲基-5-(2-甲基-1-侧氧基-2-氮杂螺[4.5]癸-7-烯-8-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.10 (s, 1H), 7.83 - 7.77 (m, 2H), 7.47 - 7.41 (m, 2H), 6.61 (s, 2H), 5.83 (s, 1H), 5.72 (d, J = 3.8 Hz, 1H), 5.55 (s, 1H), 3.58 (s, 3H), 3.32 - 3.21 (m, 2H), 2.73 (s, 3H), 2.27 (d, J = 17.4 Hz, 1H), 2.15 - 2.01 (m, 2H), 1.97 (s, 3H), 1.90 (s, 1H), 1.87 - 1.72 (m, 3H), 1.45 - 1.31 (m, 1H).	471.25
(R)-N-(4-(5-(4-(5-氮杂螺[2.4]庚烷-5-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.10 (s, 1H), 7.81 (dd, J = 8.7, 2.5 Hz, 2H), 7.43 (dd, J = 8.4, 3.6 Hz, 2H), 6.51 (s, 2H), 5.83 (s, 1H), 5.77 (s, 1H), 5.55 (s, 1H), 3.67 (t, J = 7.3 Hz, 1H), 3.58 (d, J = 1.8 Hz, 3H), 3.32 - 3.21 (m, 1H),, 2.88 (t, J = 6.0 Hz, 1H),, 2.28 (s, 2H), 1.98 (s, 3H), 1.90 (s, 2H), 1.82 (d, J = 4.4 Hz, 1H), 1.75 - 1.68 (m, 2H), 1.63 (dd, J = 15.1, 6.7 Hz, 2H), 0.63 - 0.53 (m, 4H).	511.30

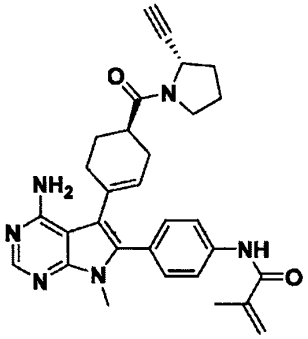
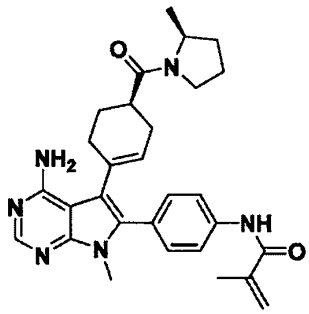
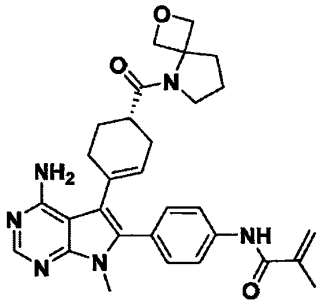
[1211]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(5-(4-(5-氮杂螺[2.4]庚烷-5-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.10 (s, 1H), 7.81 (dd, J = 8.7, 2.6 Hz, 2H), 7.43 (dd, J = 8.6, 3.5 Hz, 2H), 6.51 (s, 2H), 5.83 (s, 1H), 5.77 (s, 1H), 5.55 (s, 1H), 3.71 - 3.60 (m, 1H), 3.58 (d, J = 1.9 Hz, 3H), 3.42 (dd, J = 17.0, 11.4 Hz, 1H), 3.32 - 3.13 (m, 1H), 2.73 (q, J = 6.0 Hz, 1H), 2.28 (s, 2H), 1.98 (s, 3H), 1.90 (s, 2H), 1.82 (dt, J = 10.1, 4.6 Hz, 1H), 1.72 (td, J = 7.0, 4.0 Hz, 1H), 1.63 (dd, J = 14.8, 6.3 Hz, 2H), 0.61 (d, J = 6.4 Hz, 1H), 0.56 (d, J = 5.7 Hz, 3H).	511.35
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-氯乙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.10 (s, 1H), 7.88 - 7.75 (m, 2H), 7.57 - 7.40 (m, 2H), 6.55 (s, 1H), 5.77 (d, J = 3.1 Hz, 1H), 4.29 (s, 2H), 3.58 (s, 3H), 3.56 - 3.48 (m, 1H), 3.48 - 3.40 (m, 1H), 3.32 - 3.23 (m, 3H), 2.82 (q, J = 6.0 Hz, 1H), 2.38 - 2.10 (m, 2H), 1.87 (h, J = 6.4 Hz, 4H), 1.76 (p, J = 6.3 Hz, 2H), 1.63 (d, J = 5.9 Hz, 2H).	493.20
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-氯乙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.10 (s, 1H), 7.85 - 7.69 (m, 2H), 7.53 - 7.44 (m, 2H), 6.55 (s, 1H), 5.76 (d, J = 4.0 Hz, 1H), 4.29 (s, 2H), 3.58 (s, 3H), 3.51 (dt, J = 10.1, 6.7 Hz, 1H), 3.47 - 3.41 (m, 1H), 3.32 (d, J = 9.3 Hz, 3H), 2.83 (p, J = 5.9 Hz, 1H), 2.37 - 2.14 (m, 2H), 1.87 (p, J = 6.8 Hz, 4H), 1.76 (p, J = 6.3 Hz, 2H), 1.63 (d, J = 6.1 Hz, 2H).	493.20

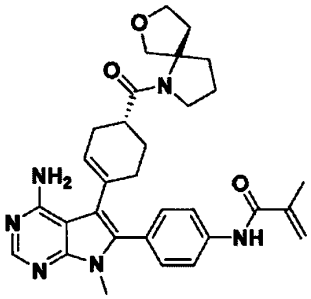
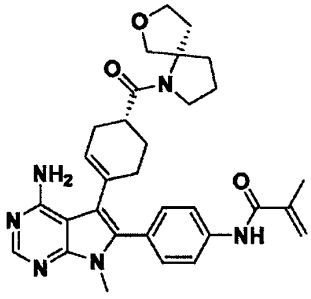
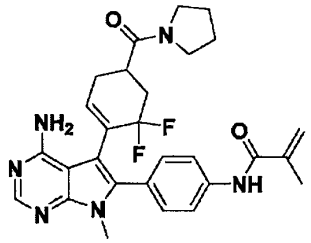
[1212]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(6-(吡咯烷-1-羰基)-5,6-二氢-2H-哌喃-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.12 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 6.63 (s, 2H), 5.94 (d, J = 4.2 Hz, 1H), 5.82 (s, 1H), 5.56 (s, 1H), 4.55 (t, J = 5.0 Hz, 1H), 3.77 (d, J = 2.9 Hz, 2H), 3.55 (s, 3H), 3.50 (s, 3H), 3.29 (td, J = 6.8, 3.1 Hz, 2H), 2.45 (d, J = 17.9 Hz, 1H), 2.31 (dt, J = 17.1, 4.2 Hz, 1H), 1.97 (s, 3H), 1.79 (dp, J = 24.9, 6.9 Hz, 4H), 1.19 (s, 1H).	487.30
(R)-N-(4-(4-氨基-7-甲基-5-(6-(吡咯烷-1-羰基)-5,6-二氢-2H-哌喃-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.11 (s, 1H), 7.85 - 7.78 (m, 2H), 7.46 - 7.39 (m, 2H), 6.55 (s, 2H), 5.94 (s, 1H), 5.85 - 5.80 (m, 1H), 5.56 (d, J = 1.8 Hz, 1H), 4.54 (t, J = 5.0 Hz, 1H), 3.77 (s, 2H), 3.55 (s, 3H), 3.52 - 3.41 (m, 2H), 3.39 - 3.28 (m, 3H), 2.43 (s, 1H), 2.29 (s, 1H), 1.97 (s, 3H), 1.77 (ddt, J = 24.2, 11.8, 5.5 Hz, 4H), 1.19 (s, 1H).	487.20
N-(4-(4-氨基-7-甲基-5-(1-(吡咯烷-1-羰基)-1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.13 (s, 1H), 7.84 - 7.78 (m, 2H), 7.46 - 7.39 (m, 2H), 6.3 (s, 1H), 5.81 (d, J = 11.2 Hz, 2H), 5.56 (s, 1H), 3.83 (d, J = 3.3 Hz, 2H), 3.57 (s, 3H), 3.23 (s, 1H), 1.97 (d, J = 1.2 Hz, 5H), 1.77 - 1.70 (m, 4H).	486.25
N-(4-(4-氨基-5-(1-(环戊烷羰基)-1,2,3,6-四氢吡啶-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.13 (s, 1H), 7.84 - 7.78 (m, 2H), 7.46 - 7.39 (m, 2H), 6.3 (s, 1H), 5.81 (d, J = 11.2 Hz, 2H), 5.56 (s, 1H), 3.83 (d, J = 3.3 Hz, 2H), 3.57 (s, 3H), 3.23 (s, 1H), 2.45 (s, 1H), 1.97 (d, J = 1.2 Hz, 5H), 1.77 - 1.70 (m, 4H).	485.25

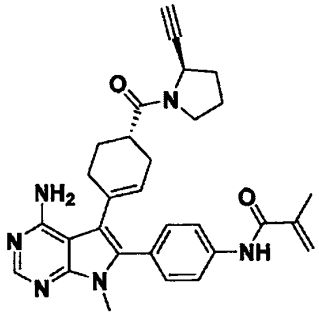
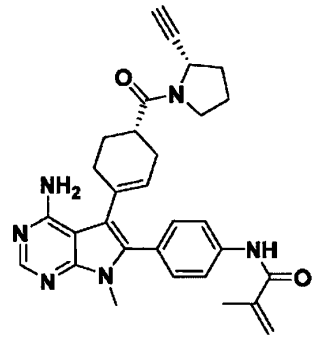
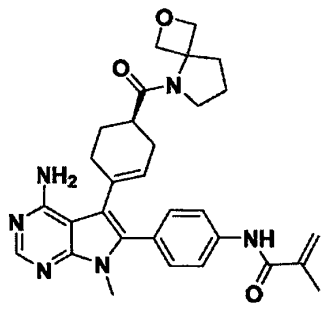
[1213]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-((R)-4-((S)-2-乙炔基吡咯烷-1-羰基)环己-1-烯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, 甲醇-d4) δ 8.15 (d, J = 3.5 Hz, 1H), 7.91-7.65 (m, 2H), 7.54-7.38 (m, 2H), 5.94 (s, 1H), 5.89-5.73 (m, 1H), 5.64-5.44 (m, 1H), 4.90-4.65 (m, 1H), 3.70-3.60 (m, 3H), 3.60-3.50 (m, 1H), 3.50-3.40 (m, 1H), 3.10-2.88 (m, 1H), 2.88-2.60 (m, 1H), 2.55-2.30 (m, 2H), 2.30-2.10 (m, 2H), 2.10-1.98 (m, 7H), 1.90-1.80 (m, 1H), 1.80-1.70 (m, 1H), 1.40-1.30 (m, 1H).	509.25
N-(4-{4-氨基-5-[(4R)-4-[(2R)-2-乙炔基吡咯烷-1-羰基]环己-1-烯-1-基]-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		1H NMR (400 MHz, 甲醇-d4) δ 8.14 (d, J = 3.4 Hz, 1H), 7.79 (dq, J = 9.1, 2.5 Hz, 2H), 7.47 (dd, J = 8.7, 2.1 Hz, 2H), 5.93 (d, J = 9.6 Hz, 1H), 5.85 (dt, J = 2.0, 1.0 Hz, 1H), 5.59 - 5.54 (m, 1H), 4.77 - 4.71 (m, 1H), 3.70 - 3.65 (m, 3H), 3.65 - 3.55 (m, 1H), 3.55 - 3.40 (m, 1H), 3.20 - 2.55 (m, 2H), 2.53 - 2.30 (m, 2H), 2.20-2.10 (m, 2H) 2.10 - 1.93 (m,7H), 1.90-1.60 (m, 2H), 1.40 - 1.30 (m,1H).	509.25
N-(4-{4-氨基-7-甲基-5-[(4S)-4-{2-氧杂-5-氮杂螺[3.4]辛烷-5-羰基}环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.11 (s, 1H), 7.84 - 7.78 (m, 2H), 7.47 - 7.38 (m, 2H), 6.48 (s, 2H), 5.83-5.79 (m, 2H), 5.56 (d, J = 2.0 Hz, 1H), 5.33-5.28 (m, 2H), 4.18 (dd, J = 4.9, 3.0 Hz, 2H), 3.58 (s, 3H), 3.55 (dt, J = 9.6, 6.1 Hz, 1H), 3.46 (dt, J = 9.6, 6.8 Hz, 1H), 2.85 (s, 1H), 2.40-2.30 (m,1H), 2.30-2.10 (m,3H),2.0-1.80 (m,5H),1.80-1.50 (m,4H).	527.30

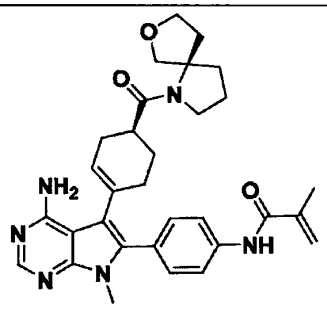
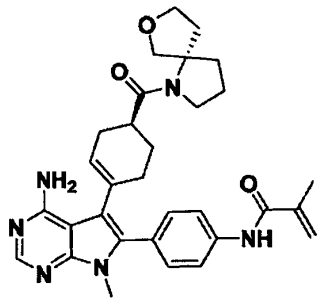
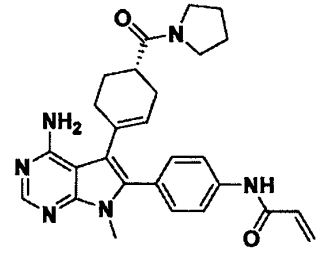
[1214]

化合物	结构	质子 NMR	MS [M+1]
N-{4-[4-氨基-7-甲基-5-(4-{7-氧杂-1-氮杂螺[4.4]壬烷-1-羰基}环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.13 (s, 1H), 7.85 - 7.72 (m, 2H), 7.52 - 7.42 (m, 2H), 5.93 (s, 1H), 5.85 (s, 1H), 5.57 (s, 1H), 4.15 (q, J = 7.7 Hz, 1H), 3.99 (d, J = 8.1 Hz, 1H), 3.92 (td, J = 7.8, 5.1 Hz, 1H), 3.66 (s, 5H), 3.53 - 3.43 (m, 1H), 2.87 (t, J = 6.0 Hz, 1H), 2.73 (ddd, J = 12.6, 7.9, 5.1 Hz, 1H), 2.38 (q, J = 19.0 Hz, 2H), 2.13 - 1.90 (m, 8H), 1.89 - 1.66 (m, 4H), 1.31 (s, 1H).	541.25
N-{4-[4-氨基-7-甲基-5-(4-{7-氧杂-1-氮杂螺[4.4]壬烷-1-羰基}环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.13 (s, 1H), 7.82 - 7.73 (m, 2H), 7.53 - 7.41 (m, 2H), 5.93 (s, 1H), 5.85 (s, 1H), 5.57 (s, 1H), 4.15 (q, J = 7.7 Hz, 1H), 3.99 (d, J = 8.1 Hz, 1H), 3.92 (td, J = 7.8, 5.1 Hz, 1H), 3.66 (s, 5H), 3.53 - 3.41 (m, 1H), 2.96 - 2.81 (m, 1H), 2.73 (ddd, J = 12.6, 7.9, 5.1 Hz, 1H), 2.38 (q, J = 19.0 Hz, 2H), 2.07 (d, J = 1.2 Hz, 3H), 2.02 (q, J = 8.5, 7.3 Hz, 3H), 1.98 - 1.81 (m, 2H), 1.81 - 1.71 (m, 4H), 1.31 (s, 1H).	541.25
N-(4-(4-氨基-5-(6,6-二氟-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.16 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.32 (s, 1H), 5.87 - 5.82 (m, 1H), 5.59 - 5.54 (m, 1H), 5.20 (s, 1H), 3.63 (s, 3H), 3.59 (s, 2H), 3.44 (t, J = 6.9 Hz, 2H), 3.40 (s, 1H), 2.47 (s, 2H), 2.31 (s, 1H), 2.09 - 1.97 (m, 5H), 2.00 - 1.87 (m, 2H).	521.30

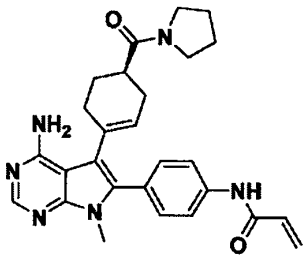
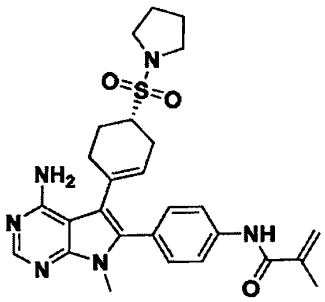
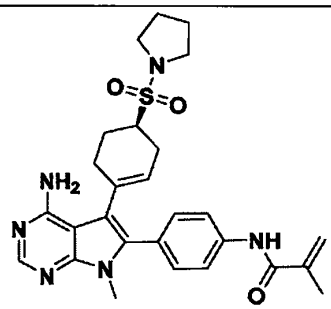
[1215]

化合物	结构	质子 NMR	MS [M+1]
N-[4-(4-氨基-5-{4-[(2R)-2-乙炔基吡咯烷-1-羰基]环己-1-烯-1-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基]-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.14 (d, J = 3.4 Hz, 1H), 7.82 - 7.74 (m, 2H), 7.47 (dt, J = 8.7, 2.1 Hz, 2H), 5.93 (d, J = 9.7 Hz, 1H), 5.85 (dt, J = 2.1, 1.0 Hz, 1H), 5.57 (d, J = 1.8 Hz, 1H), 4.74 (dd, J = 24.7, 7.0 Hz, 1H), 3.67 (d, J = 1.8 Hz, 3H), 3.59 (t, J = 8.8 Hz, 1H), 3.45 - 3.35 (m, 1H), 3.20 - 2.55 (m, 2H), 2.50 - 2.30 (m, 2H), 2.25 - 1.98 (m, 9H), 1.90-1.70 (m, 2H).	509.25
N-(4-(4-氨基-5-((S)-4-((S)-2-乙炔基吡咯烷-1-羰基)环己-1-烯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.14 (d, J = 3.4 Hz, 1H), 7.82 - 7.74 (m, 2H), 7.47 (dt, J = 8.7, 2.1 Hz, 2H), 5.93 (d, J = 9.7 Hz, 1H), 5.85 (dt, J = 2.1, 1.0 Hz, 1H), 5.57 (d, J = 1.8 Hz, 1H), 4.74 (dd, J = 24.7, 7.0 Hz, 1H), 3.67 (d, J = 1.8 Hz, 3H), 3.59 (t, J = 8.8 Hz, 1H), 3.45 - 3.35 (m, 1H), 3.20 - 2.55 (m, 2H), 2.50 - 2.30 (m, 2H), 2.25 - 1.98 (m, 9H), 1.90-1.70 (m, 2H).	509.25
N-{4-[4-氨基-7-甲基-5-(4-{2-氧杂-5-氮杂螺[3.4]辛烷-5-羰基}环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.12 (s, 1H), 7.84 - 7.77 (m, 2H), 7.47 - 7.40 (m, 2H), 6.52 (s, 1H), 5.83 (s, 1H), 5.78 (s, 1H), 5.56 (t, J = 1.5 Hz, 1H), 5.33 (d, J = 4.9 Hz, 1H), 5.28 (d, J = 4.9 Hz, 1H), 4.18 (dd, J = 4.9, 3.1 Hz, 2H), 3.59 (s, 3H), 3.57 - 3.50 (m, 1H), 3.46 (dt, J = 9.7, 6.8 Hz, 1H), 2.89 - 2.81 (m, 1H), 2.33 (s, 1H), 2.30 - 2.14 (m, 3H), 1.97 (t, J = 1.2 Hz, 3H), 1.92 -1.86 (m, 2H), 1.72 (q, J = 6.7 Hz, 2H), 1.64 (s, 2H).	527.25

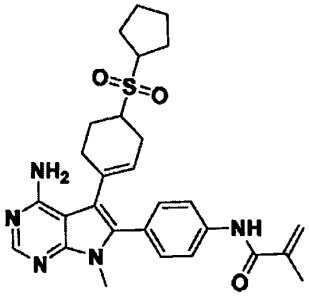
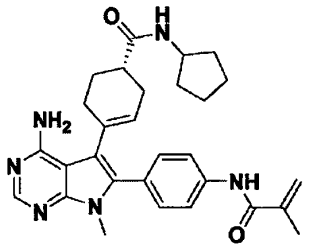
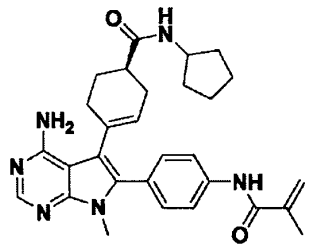
[1216]

化合物	结构	质子 NMR	MS [M+1]
N-{4-[4-氨基-7-甲基-5-(4-{7-氧杂-1-氮杂螺[4.4]壬烷-1-羰基}环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.72 - 7.65 (m, 2H), 7.62 (s, 1H), 7.47 - 7.39 (m, 2H), 6.35-5.95 (m, 2H), 5.90-5.75 (s,1H), 5.65-5.45 (m,1H),4.13 (q, *J* = 8.0 Hz, 1H), 4.02 - 3.92 (m, 2H), 3.70 (s, 3H), 3.64 (t, *J* = 8.2 Hz, 1H), 3.55 - 3.45 (m, 1H), 3.43 (d, *J* = 8.0 Hz, 1H), 2.81 (s, 1H), 2.64 (ddd, *J* = 11.5, 7.5, 3.3 Hz, 1H), 2.51 (d, *J* = 18.0 Hz, 1H), 2.35 - 2.25 (m, 1H),2.15 - 2.10(m, 3H), 2.10-1.82 (m,6H), 1.80-1.70 (m,3H).	541.30
N-{4-[4-氨基-7-甲基-5-(4-{7-氧杂-1-氮杂螺[4.4]壬烷-1-羰基}环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基]苯基}-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.32 (s, 1H), 7.76 - 7.65 (m, 3H), 7.46 - 7.39 (m, 2H), 5.96-5.87 (m, 3H), 5.54 (d, *J* = 1.7 Hz, 1H), 4.18 (q, *J* = 8.0 Hz, 1H), 3.98 (td, *J* = 8.0, 3.7 Hz, 1H), 3.88 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 3.55 (dtd, *J* = 15.7, 10.0, 9.6, 6.8 Hz, 2H), 3.42 (d, *J* = 8.0 Hz, 1H), 2.77 (tt, *J* = 7.9, 3.8 Hz, 2H), 2.59 - 2.40 (m, 1H), 2.40 - 2.25 (m, 1H),2.10 - 2.15 (m, 3H), 2.10 - 1.82 (m, 6H), 1.80 - 1.72 (m, 3H).	541.30
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.31 (s, 1H), 8.10 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.49 - 7.42 (m, 2H), 6.47 (dd, *J* = 17.0, 10.1 Hz, 2H), 6.29 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.79 (dd, *J* = 10.1, 2.1 Hz, 1H), 5.76 (s, 1H), 3.60 (s, 3H), 3.54 - 3.47 (m, 1H), 3.47 - 3.37 (m, 1H), 3.30 - 3.20 (m, 2H), 2.83 (t, *J* = 5.9 Hz, 1H), 2.26 (s, 2H), 1.91 - 1.81 (m, 4H), 1.76 (q, *J* = 6.6 Hz, 2H), 1.63 (d, *J* = 6.2 Hz, 2H).	471.20

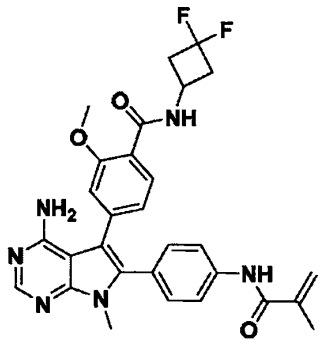
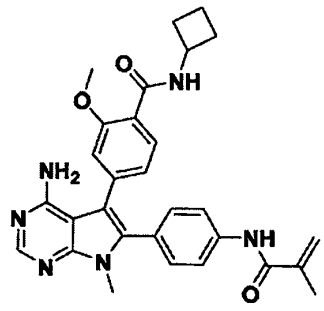
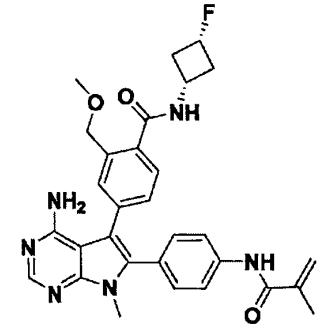
[1217]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.09 (s, 1H), 7.82 - 7.75 (m, 2H), 7.48 - 7.42 (m, 2H), 6.47 (dd, *J* = 17.0, 10.1 Hz, 2H), 6.29 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.79 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.76 (s, 1H), 3.58 (s, 3H), 3.56 - 3.47 (m, 1H), 3.47 - 3.37 (m, 1H), 3.31 - 3.20 (m, 2H), 2.82 (t, *J* = 5.9 Hz, 1H), 2.26 (s, 2H), 1.90 - 1.81 (m, 4H), 1.76 (p, *J* = 6.6 Hz, 2H), 1.63 (d, *J* = 5.7 Hz, 2H).	471.20
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-基磺酰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.96 (s, 1H), 8.13 (s, 1H), 7.81 (d, J = 2.0 Hz, 2H), 7.49 - 7.37 (m, 2H), 6.42 (s, 1H), 5.84 (s, 1H), 5.71 (d, J = 4.8 Hz, 1H), 5.55 (t, J = 1.5 Hz, 1H), 3.62 (s, 1H), 3.58 (s, 3H), 3.42 - 3.22 (m, 4H), 2.47 - 2.31 (m, 2H), 2.10 (d, J = 12.2 Hz, 1H), 2.03 - 1.90 (m, 5H), 1.90 - 1.75 (m, 4H), 1.63 (s, 1H).	521.25
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-基磺酰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.96 (s, 1H), 8.13 (s, 1H), 7.81 (d, J = 2.0 Hz, 2H), 7.49 - 7.37 (m, 2H), 6.42 (s, 1H), 5.84 (s, 1H), 5.71 (d, J = 4.8 Hz, 1H), 5.55 (t, J = 1.5 Hz, 1H), 3.62 (s, 1H), 3.58 (s, 3H), 3.42 - 3.22 (m, 4H), 2.47 - 2.31 (m, 2H), 2.10 (d, J = 12.2 Hz, 1H), 2.03 - 1.90 (m, 5H), 1.90 - 1.75 (m, 4H), 1.63 (s, 1H).	521.25

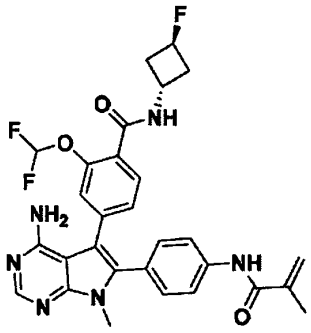
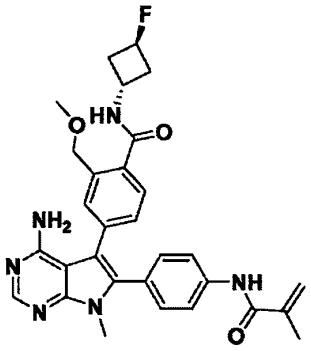
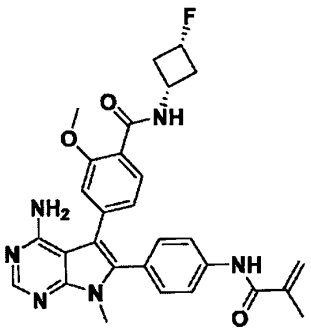
[1218]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-(环戊基磺酰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.33 (s, 1H), 7.69 (t, *J* = 8.4 Hz, 3H), 7.38 (d, *J* = 8.2 Hz, 2H), 5.92 (s, 1H), 5.87 (s, 1H), 5.55 (s, 3H), 3.68 (s, 3H), 3.50 (m, *J* = 8.2 Hz, 1H), 3.20 (d, *J* = 7.6 Hz, 1H), 2.73 (s, 1H), 2.66 (s, 1H), 2.31 (d, *J* = 15.8 Hz, 1H), 2.12 (s, 3H), 2.01 (d, *J* = 19.2 Hz, 6H), 1.85 (s, 3H), 1.70 (d, *J* = 8.4 Hz, 2H).	520.25
(S)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环戊基环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.96 (s, 1H), 8.11 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 3H), 7.43 (d, *J* = 8.6 Hz, 2H), 6.52 (s, 1H), 5.83 (s, 1H), 5.78 (s, 1H), 5.56 (s, 1H), 3.98 (q, *J* = 6.9 Hz, 1H), 3.57 (s, 3H), 2.45 (s, 1H), 2.28 (s, 1H), 2.21 (s, 1H), 1.98 (s, 3H), 1.88 (s, 2H), 1.76 (dt, *J* = 12.8, 6.6 Hz, 2H), 1.62 (dd, *J* = 12.4, 5.7 Hz, 2H), 1.47 (q, *J* = 6.8 Hz, 2H), 1.39 - 1.31 (m, 1H), 1.34 - 1.22 (m, 1H).	499.25
(R)-4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环戊基环己-3-烯-1-甲酰胺		^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.96 (s, 1H), 8.11 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 3H), 7.46 - 7.39 (m, 2H), 6.52 (s, 1H), 5.83 (s, 1H), 5.78 (s, 1H), 5.56 (s, 1H), 3.98 (q, *J* = 6.8 Hz, 1H), 3.57 (s, 3H), 2.44 (s, 1H), 2.28 (s, 1H), 2.21 (s, 1H), 1.98 (d, *J* = 1.2 Hz, 3H), 1.88 (s, 2H), 1.76 (dt, *J* = 12.5, 6.5 Hz, 2H), 1.61 (dt, *J* = 13.2, 6.0 Hz, 3H), 1.47 (q, *J* = 7.0 Hz, 2H), 1.35 (s, 2H), 1.31 (dd, *J* = 13.2, 6.9 Hz, 1H).	499.25

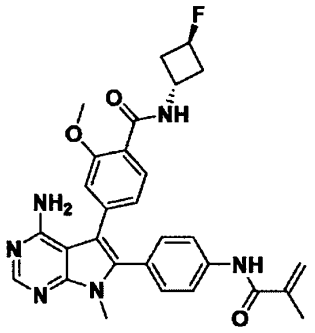
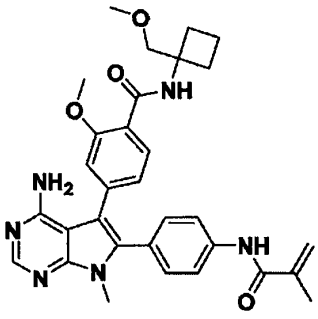
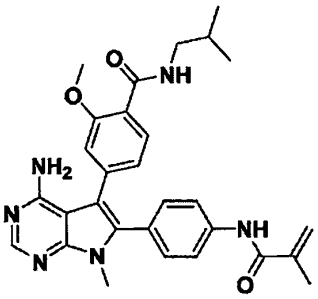
[1219]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(3,3-二氟环丁基)-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.47 (d, J = 6.8 Hz, 1H), 8.22 (s, 1H), 7.76 - 7.69 (m, 2H), 7.62 (d, J = 7.9 Hz, 1H), 7.35 - 7.27 (m, 2H), 6.93 (d, J = 1.5 Hz, 1H), 6.87 (dd, J = 7.8, 1.5 Hz, 1H), 6.01 (s, 1H), 5.81 (s, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.30 - 4.21 (m, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.00 - 2.85 (m, 2H), 2.82 - 2.68 (m, 2H), 2.08 (s, 1H), 1.96 (d, J = 1.2 Hz, 3H).	547.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环丁基-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.23 (d, J = 11.7 Hz, 2H), 7.76 - 7.68 (m, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.34 - 7.26 (m, 2H), 6.92 (d, J = 1.5 Hz, 1H), 6.85 (dd, J = 7.9, 1.5 Hz, 1H), 6.01 (s, 1H), 5.81 (d, J = 1.3 Hz, 1H), 5.57 - 5.51 (m, 1H), 4.39 (h, J = 8.2 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 2.21 (dtt, J = 8.9, 6.9, 3.0 Hz, 2H), 2.06 - 1.93 (m, 5H), 1.66 (tt, J = 10.5, 6.3 Hz, 2H).	511.45
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1s,3s)-3-氟环丁基)-2-(甲氧基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.65 (d, J = 6.9 Hz, 1H), 8.21 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.20 (dd, J = 7.9, 1.8 Hz, 1H), 5.85 (s, 1H), 5.79 (s, 1H), 5.54 (s, 1H), 5.32 - 5.14 (m, 1H), 4.51 (s, 2H), 4.45 (s, 1H), 3.60 (s, 3H), 3.16 (s, 3H), 2.53 - 2.35 (m, 4H), 1.95 (s, 3H).	543.25

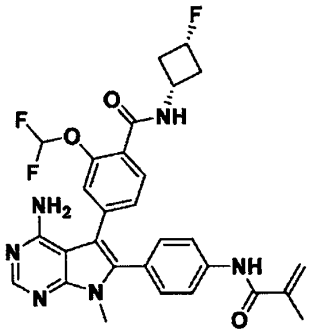
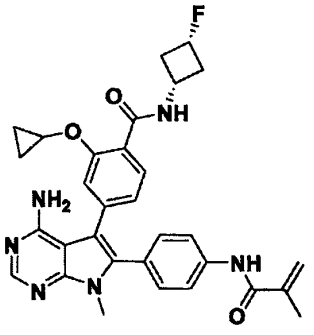
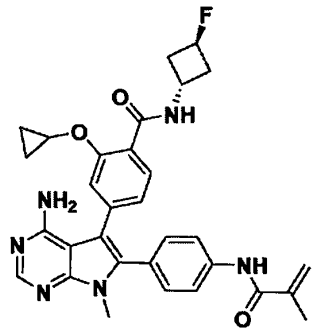
[1220]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-(二氟甲氧基)-N-((1r,3r)-3-氟环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.62 (d, J = 7.0 Hz, 1H), 8.22 (s, 1H), 7.78 - 7.70 (m, 2H), 7.47 (d, J = 7.9 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.17 - 7.01 (m, 3H), 6.01 (s, 2H), 5.80 (d, J = 1.3 Hz, 1H), 5.55 (d, J = 1.7 Hz, 1H), 5.31 (ddd, J = 10.5, 6.4, 4.2 Hz, 1H), 5.17 (ddd, J = 11.0, 6.6, 4.3 Hz, 1H), 3.59 (s, 3H), 2.55 (dd, J = 9.2, 4.2 Hz, 1H), 2.51 - 2.29 (m, 2H), 1.95 (d, J = 1.2 Hz, 3H).	565.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1r,3r)-3-氟环丁基)-2-(甲氧基甲基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.62 (d, J = 7.5 Hz, 1H), 8.21 (s, 1H), 7.71 (dd, J = 8.7, 2.2 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.20 (dd, J = 7.8, 1.8 Hz, 1H), 5.98 (s, 1H), 5.79 (s, 1H), 5.54 (d, J = 2.0 Hz, 1H), 4.92 - 4.78 (p, J = 6.8 Hz, 1H), 4.51 (s, 2H), 3.92 (p, J = 7.9 Hz, 1H), 3.60 (s, 3H), 3.16 (s, 3H), 2.73 (ddq, J = 12.7, 6.0, 3.1 Hz, 2H), 2.29 - 2.11 (m, 2H), 1.95 (d, J = 1.2 Hz, 3H).	543.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1s,3s)-3-氟环丁基)-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.32 (d, J = 7.7 Hz, 1H), 8.21 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 6.92 (s, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.01 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 5.02 - 4.65 (m, 1H), 3.96 (q, J = 8.0 Hz, 1H), 3.66 (d, J = 43.5 Hz, 6H), 2.72 (dd, J = 11.6, 5.5 Hz, 2H), 2.37 - 2.11 (m, 2H), 1.95 (s, 3H).	529.25

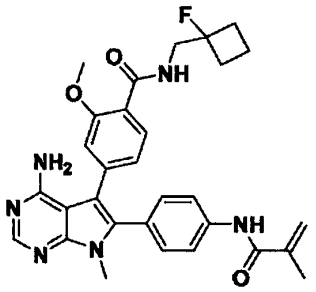
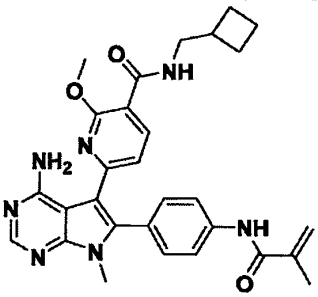
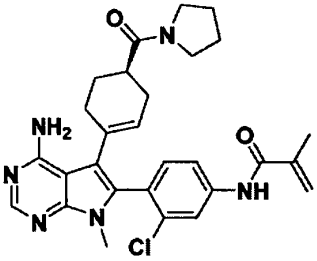
[1221]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1r,3r)-3-氟环丁基)-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.32 (d, J = 7.7 Hz, 1H), 8.21 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 6.92 (s, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.01 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 5.02 - 4.65 (m, 1H), 3.96 (q, J = 8.0 Hz, 1H), 3.66 (d, J = 43.5 Hz, 6H), 2.72 (dd, J = 11.6, 5.5 Hz, 2H), 2.37 - 2.11 (m, 2H), 1.95 (s, 3H).	529.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-甲氧基-N-(1-(甲氧基甲基)环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.40 (s, 1H), 8.14 (s, 1H), 7.75 (t, J = 8.1 Hz, 3H), 7.35 - 7.27 (m, 2H), 7.04- 6.99 (m, 1H), 6.86 (dd, J = 7.9, 1.5 Hz, 1H), 5.81 (s, 1H), 5.55 (d, J = 1.6 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.58 (s, 2H), 3.33 (s,3H),2.43 - 2.33 (m, 2H), 2.07 (s, 2H), 1.95 (d, J = 1.5 Hz, 3H), 1.93 - 1.72 (m, 2H).	555.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-异丁基-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.21 (s, 1H), 8.10 (t, J = 5.9 Hz, 1H), 7.76 - 7.69 (m, 2H), 7.65 (d, J = 7.9 Hz, 1H), 7.34 - 7.27 (m, 2H), 6.94 (d, J = 1.5 Hz, 1H), 6.86 (dd, J = 7.9, 1.5 Hz, 1H), 6.02 (s, 1H), 5.81 (s, 1H), 5.54 (d, J = 1.9 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 3.10 (t, J = 6.4 Hz, 2H), 1.95 (t, J = 1.2 Hz, 3H), 1.81 (hept, J = 6.7 Hz, 1H), 0.89 (d, J = 6.7 Hz, 6H).	513.30

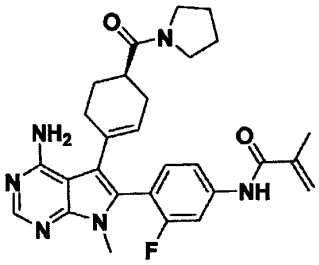
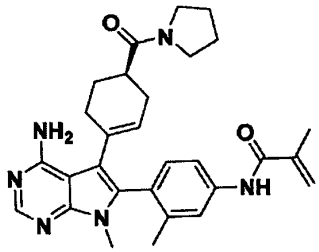
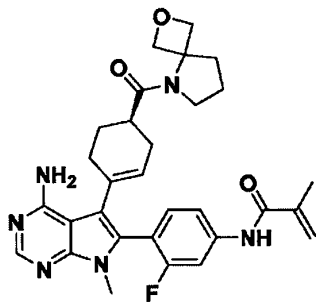
[1222]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-(二氟甲氧基)-N-((1s,3s)-3-氟环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.58 (d, J = 7.7 Hz, 1H), 8.22 (s, 1H), 7.74-7.73 (d, J = 6.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.13-6.84 (dd, J = 7.9, 1.6 Hz, 3H), 6.03 (s, 1H), 5.80 (s, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.78 (p, J = 7.0 Hz, 1H), 3.93 (q, J = 8.0 Hz, 1H), 3.59 (s, 3H), 2.73 (dq, J = 9.6, 3.0 Hz, 1H), 2.27 - 2.06 (m, 2H), 1.95 (t, J = 1.2 Hz, 3H),	565.20
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-环丙氧基-N-((1s,3s)-3-氟环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 (s, 1H), 8.16 (d, J = 7.0 Hz, 1H), 7.81 - 7.66 (m, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.39 - 7.28 (m, 2H), 7.23 (d, J = 1.6 Hz, 1H), 6.91 (dd, J = 7.8, 1.5 Hz, 1H), 5.85 - 5.75 (m, 1H), 5.58 - 5.51 (m, 1H), 5.23 (dddd, J = 56.7, 10.2, 6.5, 3.8 Hz, 1H), 4.48 (q, J = 7.7 Hz, 1H), 3.73 (tt, J = 6.1, 3.0 Hz, 1H), 3.61 (s, 3H), 2.48 - 2.38 (m, 2H), 2.38 - 2.28 (m, 2H), 1.96 (t, J = 1.3 Hz, 3H), 0.66 (t, J = 5.8 Hz, 2H), 0.61 (d, J = 3.2 Hz, 2H).	555.25
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-环丙氧基-N-((1r,3r)-3-氟环丁基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 (s, 1H), 8.12 (d, J = 7.7 Hz, 1H), 7.82 - 7.67 (m, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.22 (d, J = 1.5 Hz, 1H), 6.90 (dd, J = 7.9, 1.5 Hz, 1H), 5.81 (t, J = 1.1 Hz, 1H), 5.54 (t, J = 1.4 Hz, 1H), 4.84 (dp, J = 56.8, 6.8 Hz, 1H), 3.92 (dt, J = 15.3, 7.6 Hz, 1H), 3.72 (dq, J = 6.2, 3.0 Hz, 1H), 3.61 (s, 3H), 2.81 - 2.64 (m, 2H), 2.29 - 2.03 (m, 2H), 1.95 (t, J = 1.2 Hz, 3H), 0.64 (dd, J = 24.4, 4.7 Hz, 4H).	555.30

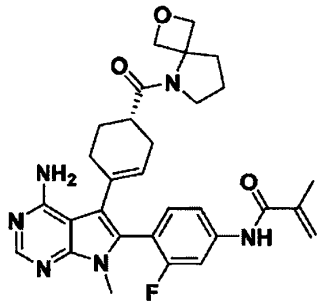
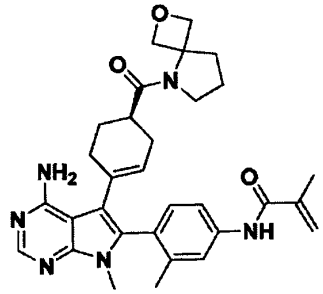
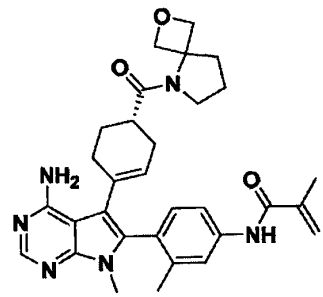
[1223]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-氟环丁基)甲基)-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.24 (d, J = 18.2 Hz, 2H), 7.75 - 7.68 (m, 3H), 7.33 - 7.27 (m, 2H), 6.95 (d, J = 1.4 Hz, 1H), 6.87 (dd, J = 7.9, 1.5 Hz, 1H), 6.04 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.73 (s, 3H), 3.71 - 3.60 (m, 2H), 3.60 (s, 3H), 2.26 - 2.13 (m, 4H), 2.08 (s, 1H), 1.95 (t, J = 1.2 Hz, 3H), 1.75 (dd, J = 11.4, 6.3 Hz, 1H), 1.53 (q, J = 8.8 Hz, 1H).	543.30
6-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-(环丁基甲基)-2-甲氧基烟碱酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.99 (s, 1H), 8.18 (d, J = 11.9 Hz, 2H), 7.86 - 7.69 (m, 3H), 7.40 - 7.28 (m, 4H), 6.55 (d, J = 7.9 Hz, 1H), 5.83 (s, 1H), 5.56 (d, J = 1.9 Hz, 1H), 4.03 (s, 3H), 3.55 (s, 3H), 3.28 (d, J = 6.3 Hz, 2H), 2.53 (s, 1H), 1.82 (q, J = 6.7, 6.2 Hz, 2H), 1.77 - 1.67 (m, 2H).	526.30
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氯苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.11 (d, J = 3.9 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.74 (ddd, J = 8.4, 3.5, 2.1 Hz, 1H), 7.37 (dd, J = 8.4, 6.3 Hz, 1H), 6.55 (d, J = 47.7 Hz, 2H), 5.87 (s, 1H), 5.75 - 5.63 (m, 1H), 5.60 (s, 1H), 3.51 - 3.41 (m, 2H), 3.40 (d, J = 2.0 Hz, 3H), 3.27 (ddt, J = 12.1, 8.4, 4.6 Hz, 2H), 2.75 (qt, J = 7.7, 3.4 Hz, 1H), 2.34 - 2.03 (m, 3H), 1.97 (s, 4H), 1.84 (qd, J = 6.7, 3.3 Hz, 2H), 1.76 (qd, J = 6.7, 2.2 Hz, 2H), 1.71 - 1.45 (m, 2H).	519.20

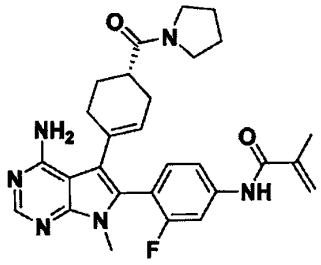
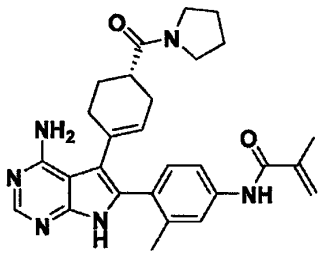
[1224]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.12 (s, 1H), 7.83 (dd, J = 12.6, 2.0 Hz, 1H), 7.59 (dd, J = 8.4, 2.1 Hz, 1H), 7.37 (t, J = 8.5 Hz, 1H), 6.57 (s, 2H), 5.86 (s, 1H), 5.69 (s, 1H), 5.60 (s, 1H), 3.55 - 3.40 (m, 5H), 3.28 (d, J = 6.5 Hz, 1H), 2.79 (t, J = 6.1 Hz, 1H), 2.21 (d, J = 17.2 Hz, 2H), 1.97 (d, J = 1.3 Hz, 3H), 1.81 (dq, J = 35.8, 6.8 Hz, 4H), 1.63 (s, 2H).	503.25
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.10 (s, 1H), 7.71 (t, J = 2.7 Hz, 1H), 7.62 (ddd, J = 8.0, 5.6, 2.2 Hz, 1H), 7.18 (dd, J = 8.3, 6.6 Hz, 1H), 6.48 (d, J = 17.0 Hz, 2H), 5.91 - 5.79 (m, 1H), 5.66 (ddt, J = 14.5, 4.1, 2.2 Hz, 1H), 5.54 (t, J = 1.5 Hz, 1H), 3.56 - 3.39 (m, 2H), 3.34 (s, 3H), 3.27 (q, J = 6.9 Hz, 2H), 2.73 (p, J = 6.3 Hz, 1H), 2.21 (q, J = 15.7, 12.1 Hz, 2H), 2.06 (s, 3H), 2.01 - 1.80 (m, 7H), 1.80 - 1.70 (m, 2H), 1.56 (q, J = 7.9, 7.0 Hz, 2H).	499.35
(R)-N-(4-(5-(4-(2-氧杂-5-氮杂螺[3.4]辛烷-5-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.14 (s, 1H), 7.84 (dd, J = 12.6, 2.0 Hz, 1H), 7.59 (dd, J = 8.4, 2.0 Hz, 1H), 7.37 (t, J = 8.5 Hz, 1H), 6.55 (s, 2H), 5.86 (t, J = 1.1 Hz, 1H), 5.71 (s, 1H), 5.60 (d, J = 1.9 Hz, 1H), 5.30 (dd, J = 13.7, 4.9 Hz, 2H), 4.19 (d, J = 4.9 Hz, 2H), 3.60 - 3.43 (m, 5H), 2.97 - 2.78 (m, 1H), 2.44 - 2.07 (m, 4H), 1.98 (t, J = 1.2 Hz, 5H), 1.70 (dq, J = 19.5, 7.6, 7.1 Hz, 4H).	545.25

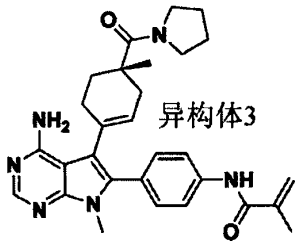
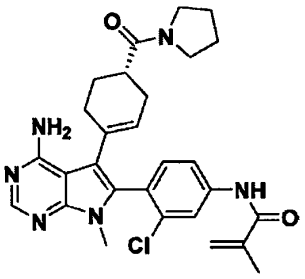
[1225]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(5-(4-(2-氧杂-5-氮杂螺[3.4]辛烷-5-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.14 (s, 1H), 7.84 (dd, J = 12.6, 2.0 Hz, 1H), 7.59 (dd, J = 8.5, 2.0 Hz, 1H), 7.37 (t, J = 8.5 Hz, 1H), 6.55 (s, 2H), 5.86 (t, J = 1.0 Hz, 1H), 5.71 (s, 1H), 5.60 (d, J = 1.8 Hz, 1H), 5.30 (dd, J = 13.7, 4.9 Hz, 2H), 4.19 (d, J = 4.9 Hz, 2H), 3.61 - 3.40 (m, 5H), 2.93 - 2.78 (m, 1H), 2.37 - 2.13 (m, 4H), 1.98 (t, J = 1.2 Hz, 5H), 1.70 (td, J = 15.9, 14.6, 7.9 Hz, 4H).	545.25
(R)-N-(4-(5-(4-(2-氧杂-5-氮杂螺[3.4]辛烷-5-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.11 (s, 1H), 7.73-7.70 (m, 1H), 7.63-7.62 (m, 1H), 7.20-7.17 (m, 1H), 6.51 (d, J = 28.6 Hz, 2H), 5.83 (s, 1H), 5.68 (d, J = 10.9 Hz, 1H), 5.55 (t, J = 1.5 Hz, 1H), 5.31-5.26 (m, 2H), 4.18-4.17 (m, 2H), 3.54 - 3.47 (m, 1H), 3.47 - 3.38 (m, 1H), 3.34 (s, 3H), 2.74 (d, J = 12.8 Hz, 1H), 2.35- 2.24 (m, 1H), 2.23 - 2.16 (m, 3H), 2.06 (s, 3H), 1.97 (t, J = 1.2 Hz, 4H), 1.93 - 1.79 (m, 1H), 1.70 (p, J = 6.7 Hz, 2H), 1.58 (d, J = 5.2 Hz, 2H).	541.35
(S)-N-(4-(5-(4-(2-氧杂-5-氮杂螺[3.4]辛烷-5-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.11 (s, 1H), 7.73-7.70 (m, 1H), 7.63-7.62 (m, 1H), 7.20-7.17 (m, 1H), 6.51 (d, J = 28.6 Hz, 2H), 5.83 (s, 1H), 5.68 (d, J = 10.9 Hz, 1H), 5.55 (t, J = 1.5 Hz, 1H), 5.31-5.26 (m, 2H), 4.18-4.17 (m, 2H), 3.54 - 3.47 (m, 1H), 3.47 - 3.38 (m, 1H), 3.34 (s, 3H), 2.74 (d, J = 12.8 Hz, 1H), 2.35- 2.24 (m, 1H), 2.23 - 2.16 (m, 3H), 2.06 (s, 3H), 1.97 (t, J = 1.2 Hz, 4H), 1.93 - 1.79 (m, 1H), 1.70 (p, J = 6.7 Hz, 2H), 1.58 (d, J = 5.2 Hz, 2H).	541.30

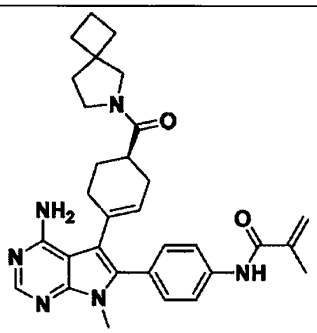
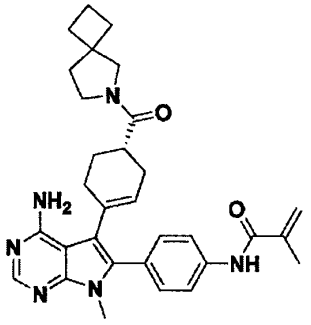
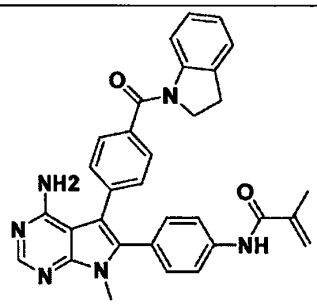
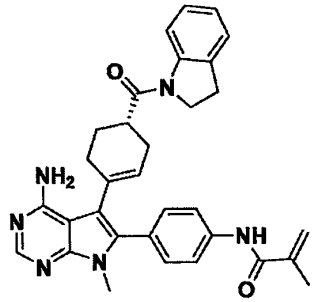
[1226]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.12 (s, 1H), 7.83 (dd, J = 12.5, 2.0 Hz, 1H), 7.59 (dd, J = 8.5, 2.0 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 6.60 (s, 2H), 5.86 (s, 1H), 5.69 (s, 1H), 5.60 (s, 1H), 3.55 - 3.40 (m, 5H), 3.28 (d, J = 6.5 Hz, 1H), 2.83 - 2.76 (m, 1H), 2.21 (d, J = 16.9 Hz, 2H), 1.98 (t, J = 1.2 Hz, 3H), 1.87 (p, J = 6.8 Hz, 2H), 1.76 (p, J = 6.8 Hz, 2H), 1.63 (s, 2H).	503.25
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.10 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.61 (t, J = 8.2, 2.3 Hz, 1H), 7.18 (t, J = 8.3, 6.6 Hz, 1H), 6.50 (s, 2H), 5.87 - 5.78 (m, 1H), 5.64 (s, 1H), 5.54 (d, J = 1.8 Hz, 1H), 3.52 - 3.38 (m, 2H), 3.33 - 3.22 (m, 5H), 2.73 (t, J = 6.1 Hz, 1H), 2.25 (t, J = 42.5, 23.2 Hz, 2H), 2.06 (s, 3H), 1.97 (d, J = 1.2 Hz, 4H), 1.93 - 1.80 (m, 3H), 1.75 (p, J = 6.7 Hz, 2H), 1.56 (d, J = 6.1 Hz, 2H).	499.30
(S)-N-(4-(4-氨基-7-甲基-5-(4-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.12 (s, 1H), 7.80 - 7.72 (m, 2H), 7.32 - 7.24 (m, 2H), 5.86 - 5.78 (m, 2H), 5.76 (s, 2H), 5.56 - 5.51 (m, 1H), 3.58 (s, 3H), 3.39 (s, 4H), 2.74 (d, J = 16.0 Hz, 1H), 2.05 - 1.82 (m, 7H), 1.77 - 1.55 (m, 5H), 1.16 (s, 3H).	499.30
(S)-N-(4-(4-氨基-7-甲基-5-(4-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.13 (s, 1H), 7.80 - 7.72 (m, 2H), 7.32 - 7.24 (m, 2H), 6.05 - 5.65 (m, 3H), 5.56 - 5.51 (m, 1H), 3.59 (s, 3H), 3.41 (s, 4H), 2.75 (d, J = 16.7 Hz, 1H), 2.08 - 1.89 (m, 7H), 1.75 (s, 4H), 1.63 (dd, J = 12.6, 6.4 Hz, 1H), 1.16 (s, 3H).	499.30

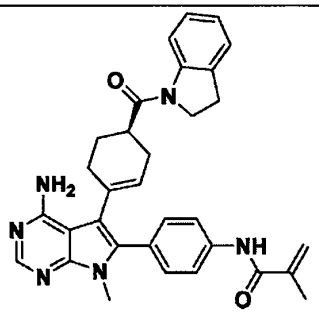
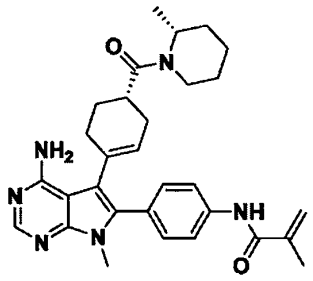
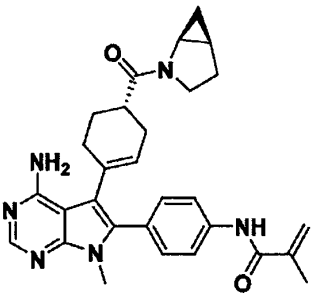
[1227]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(4-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.08 (s, 1H), 7.84 - 7.76 (m, 2H), 7.45 - 7.37 (m, 2H), 6.53 (s, 2H), 5.83 (s, 1H), 5.78 (d, J = 4.5 Hz, 1H), 5.56 (t, J = 1.5 Hz, 1H), 3.57 (s, 4H), 3.33 (s, 3H), 2.77 (d, J = 14.8 Hz, 1H), 2.11 (d, J = 13.6 Hz, 1H), 1.98 (d, J = 1.2 Hz, 3H), 1.90 (d, J = 17.3 Hz, 1H), 1.77 (s, 6H), 1.44 (s, 1H), 1.21 (s, 3H).	499.30
(S)-N-(4-(4-氨基-7-甲基-5-(4-甲基-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.08 (s, 1H), 7.84 - 7.77 (m, 2H), 7.45 - 7.37 (m, 2H), 6.52 (s, 2H), 5.83 (t, J = 1.1 Hz, 1H), 5.81 - 5.75 (m, 1H), 5.56 (t, J = 1.5 Hz, 1H), 3.57 (s, 4H), 3.50 (s, 3H), 2.82 - 2.73 (m, 1H), 2.12 (d, J = 13.7 Hz, 1H), 1.97 (t, J = 1.2 Hz, 3H), 1.90 (d, J = 17.1 Hz, 1H), 1.77 (s, 6H), 1.70 - 1.37 (m, 1H), 1.21 (s, 3H).	499.30
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氯苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.15 - 8.03 (m, 2H), 7.74 (ddd, J = 8.4, 3.6, 2.2 Hz, 1H), 7.37 (dd, J = 8.4, 6.4 Hz, 1H), 6.55 (d, J = 48.7 Hz, 2H), 5.87 (s, 1H), 5.78 - 5.60 (m, 2H), 3.54 - 3.41 (m, 2H), 3.40 (d, J = 2.0 Hz, 3H), 3.27 (ddt, J = 12.1, 8.4, 4.5 Hz, 2H), 2.75 (tt, J = 9.5, 4.2 Hz, 1H), 2.36 - 2.03 (m, 3H), 1.97 (s, 4H), 1.84 (qd, J = 6.7, 3.3 Hz, 2H), 1.76 (qd, J = 6.8, 2.2 Hz, 2H), 1.70 - 1.44 (m, 2H).	519.20

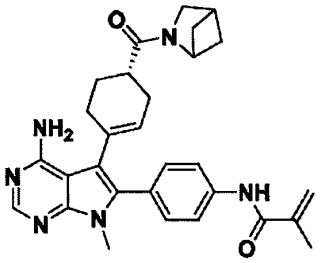
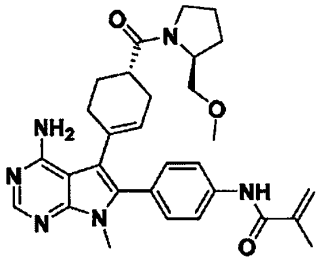
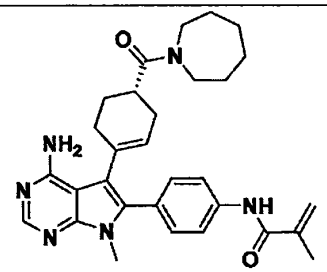
[1228]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(5-(4-(6-氮杂螺[3.4]辛烷-6-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, 甲醇-d4) 8.14 (s, 1H), 7.81 -7.75 (m, 2H), 7.49 - 7.43 (m, 2H), 5.93 (s, 1H), 5.85 (t, J = 0.9 Hz, 1H), 5.57 (d, J = 1.7 Hz, 1H), 3.66 (s, 3H), 3.64 - 3.49 (m, 2H), 3.28 - 3.17 (m, 2H), 2.88 - 2.80 (m, 1H), 2.43 (t, J = 11.5 Hz, 1H), 2.35 (s, 1H), 2.16 - 1.98 (m, 7H), 1.96 - 1.86 (s, 1H), 1.86 - 1.68 (s, 7H), 1.28 (s, 1H).	525.30
(S)-N-(4-(5-(4-(6-氮杂螺[3.4]辛烷-6-羰基)环己-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, 甲醇-d4) 8.14 (s, 1H), 7.82 - 7.74 (m, 2H), 7.46 (d, J = 8.2 Hz, 2H), 5.93 (s, 1H), 5.85 (t, J = 1.0 Hz, 1H), 5.57 (d, J = 1.5 Hz, 1H), 3.66 (s, 3H), 3.64 - 3.50 (m, 2H), 3.28 - 3.17 (m, 2H), 2.84 (t, J = 6.2 Hz, 1H), 2.42 (s, 1H), 2.35 (s, 1H), 2.16 - 1.98 (m, 7H), 1.96 - 1.85 (m, 1H), 1.81 (q, J = 6.6 Hz, 2H), 1.76 (s, 5H), 1.28 (s, 1H).	525.30
N-(4-(4-氨基-5-(4-(吲哚啉-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 (s, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.35 - 7.24 (m, 5H), 7.16 (s, 1H), 7.02 (s, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 4.05 (t, J = 8.3 Hz, 2H), 3.62 (s, 3H), 3.08 (t, J = 8.2 Hz, 2H), 1.95 (d, J = 1.3 Hz, 3H).	529.25
(S)-N-(4-(4-氨基-5-(4-(吲哚啉-1-羰基)环己-1-烯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.13 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.52 - 7.39 (m, 2H), 7.23 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 7.7 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.57 (s, 2H), 5.83 (d, J = 7.2 Hz, 2H), 5.55 (s, 1H), 4.32 - 4.02 (m, 2H), 3.59 (s, 3H), 3.14 (t, J = 8.5 Hz, 2H), 3.01 (s, 1H), 2.37 (s, 2H), 1.98 (t, J = 1.2 Hz, 5H), 1.75 (s, 2H).	533.25

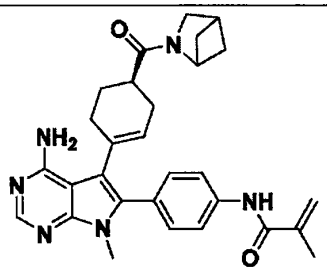
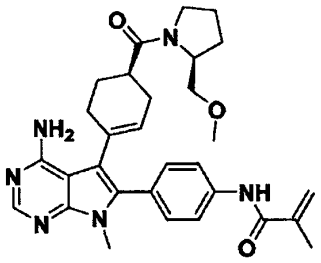
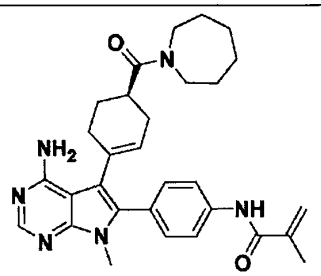
[1229]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-5-(4-(吲哚啉-1-羰基)环己-1-烯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.13 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.52 - 7.39 (m, 2H), 7.23 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 7.7 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.57 (s, 2H), 5.83 (d, J = 7.2 Hz, 2H), 5.55 (s, 1H), 4.32 - 4.02 (m, 2H), 3.59 (s, 3H), 3.14 (t, J = 8.5 Hz, 2H), 3.01 (s, 1H), 2.37 (s, 2H), 1.98 (t, J = 1.2 Hz, 5H), 1.75 (s, 2H).	533.30
N-(4-(4-氨基-7-甲基-5-((S)-4-((R)-2-甲基哌啶-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.10 (s, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 6.54 (s, 2H), 5.83 (s, 1H), 5.79 - 5.71 (m, 1H), 5.55 (s, 1H), 4.74 (s, 1H), 4.30 (s, 1H), 3.58 (s, 3H), 3.05 (dd, J = 31.8, 9.0 Hz, 2H), 2.36 - 2.11 (m, 2H), 1.97 (s, 3H), 1.87 - 1.70 (m, 2H), 1.72 - 1.34 (m, 7H), 1.35 - 1.12 (m, 2H), 1.05 (d, J = 6.9 Hz, 2H).	513.30
N-(4-(5-((S)-4-((1S,5R)-2-氮杂双环[3.1.0]己烷-2-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (d, J = 2.1 Hz, 1H), 8.10 (s, 1H), 7.81 (dt, J = 8.8, 2.2 Hz, 2H), 7.49 - 7.40 (m, 2H), 6.55 (s, 1H), 5.84 (t, J = 1.0 Hz, 1H), 5.78 (d, J = 9.9 Hz, 1H), 5.56 (d, J = 1.7 Hz, 1H), 3.80 - 3.65 (m, 1H), 3.59 (s, 4H), 3.17 (dd, J = 19.5, 9.2 Hz, 1H), 2.96 (dt, J = 12.5, 8.6 Hz, 1H), 2.44 - 2.20 (m, 2H), 2.19 - 1.99 (m, 1H), 1.98 (d, J = 1.2 Hz, 3H), 1.95 - 1.73 (m, 3H), 1.75 - 1.48 (m, 2H), 0.85 - 0.67 (m, 1H), 0.61 - 0.47 (m, 1H).	497.25

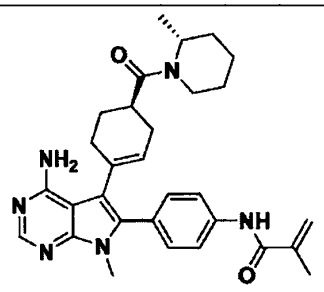
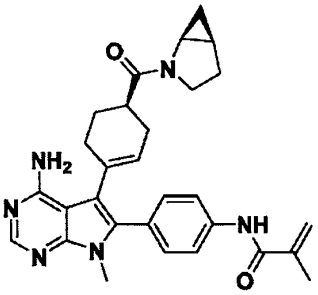
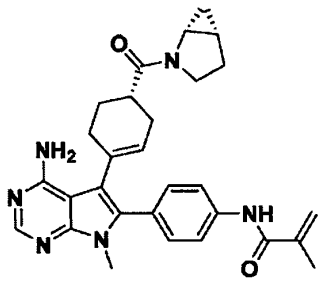
[1230]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(5-(4-(2-氮杂双环[2.1.1]己烷-2-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.95 (d, J = 1.8 Hz, 1H), 8.10 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 8.7, 2.2 Hz, 2H), 7.43 (dd, J = 8.7, 3.1 Hz, 2H), 6.55 (s, 1H), 5.83 (s, 1H), 5.77 (d, J = 6.0 Hz, 1H), 5.55 (s, 1H), 4.56 (dd, J = 21.1, 7.0 Hz, 1H), 3.58 (s, 3H), 3.51 - 3.41 (m, 1H), 3.24 (d, J = 4.3 Hz, 1H), 2.98 - 2.78 (m, 2H), 2.73 (q, J = 6.1 Hz, 1H), 2.37 - 2.13 (m, 2H), 1.98 (d, J = 1.2 Hz, 4H), 1.90 (s, 3H), 1.66 (d, J = 6.2 Hz, 1H), 1.58 (s, 1H), 1.38 - 1.19 (m, 2H).	497.25
N-(4-(4-氨基-5-((S)-4-((S)-2-(甲氧基甲基)吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.94 (s, 1H), 8.10 (d, J = 5.0 Hz, 1H), 7.84 - 7.76 (m, 2H), 7.53 - 7.39 (m, 2H), 6.59 (s, 2H), 5.85 - 5.81 (m, 1H), 5.77 (s, 1H), 5.55 (d, J = 1.7 Hz, 1H), 4.08 (dd, J = 7.4, 3.7 Hz, 1H), 3.58 (s, 3H), 3.56 - 3.47 (m, 1H), 3.46 - 3.35 (m, 2H), 3.28 (d, J = 4.0 Hz, 1H), 3.18 (s, 3H), 2.93 - 2.81 (m, 1H), 2.39 - 2.27 (m, 0H), 2.20 (d, J = 18.4 Hz, 1H), 1.98 (t, J = 1.3 Hz, 3H), 1.95 - 1.74 (m, 6H), 1.63 (d, J = 18.3 Hz, 2H).	529.30
(S)-N-(4-(4-氨基-5-(4-(氮杂环庚烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.10 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 6.52 (s, 2H), 5.83 (s, 1H), 5.76 (s, 1H), 5.55 (s, 1H), 3.58 (s, 3H), 3.55 - 3.33 (m, 4H), 2.96 (s, 1H), 2.24 (t, J = 17.8 Hz, 2H), 1.97 (d, J = 1.3 Hz, 3H), 1.92 (s, 1H), 1.87 (s, 1H), 1.67 (d, J = 6.0 Hz, 2H), 1.61 (d, J = 6.5 Hz, 4H), 1.48 (s, 4H).	513.35

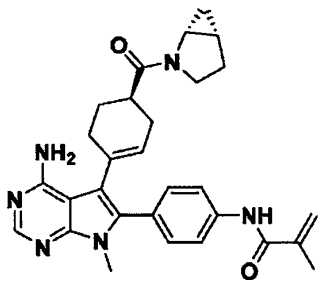
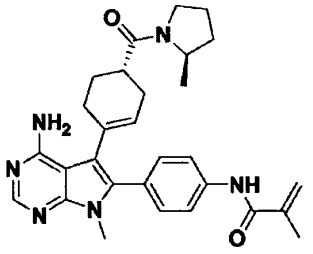
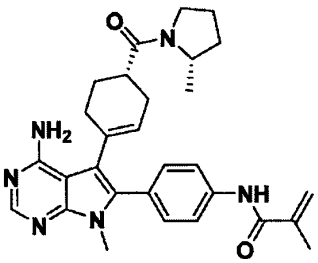
[1231]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(5-(4-(2-氮杂双环[2.1.1]己烷-2-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.95 (d, J = 1.8 Hz, 1H), 8.10 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 8.7, 2.2 Hz, 2H), 7.43 (dd, J = 8.7, 3.1 Hz, 2H), 6.55 (s, 1H), 5.83 (s, 1H), 5.77 (d, J = 6.0 Hz, 1H), 5.55 (s, 1H), 4.56 (dd, J = 21.1, 7.0 Hz, 1H), 3.58 (s, 3H), 3.51 - 3.41 (m, 1H), 3.24 (d, J = 4.3 Hz, 1H), 2.98 - 2.78 (m, 2H), 2.73 (q, J = 6.1 Hz, 1H), 2.37 - 2.13 (m, 2H), 1.98 (d, J = 1.2 Hz, 4H), 1.90 (s, 3H), 1.66 (d, J = 6.2 Hz, 1H), 1.58 (s, 1H), 1.38 - 1.19 (m, 2H).	497.25
N-(4-(4-氨基-5-((R)-4-((S)-2-(甲氧基甲基)吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.94 (s, 1H), 8.10 (d, J = 5.0 Hz, 1H), 7.84 - 7.76 (m, 2H), 7.53 - 7.39 (m, 2H), 6.59 (s, 2H), 5.85 - 5.81 (m, 1H), 5.77 (s, 1H), 5.55 (d, J = 1.7 Hz, 1H), 4.08 (dd, J = 7.4, 3.7 Hz, 1H), 3.58 (s, 3H), 3.56 - 3.47 (m, 1H), 3.46 - 3.35 (m, 2H), 3.28 (d, J = 4.0 Hz, 1H), 3.18 (s, 3H), 2.93 - 2.81 (m, 1H), 2.39 - 2.27 (m, 0H), 2.20 (d, J = 18.4 Hz, 1H), 1.98 (t, J = 1.3 Hz, 3H), 1.95 - 1.74 (m, 6H), 1.63 (d, J = 18.3 Hz, 2H).	529.30
(R)-N-(4-(4-氨基-5-(4-(氮杂环庚烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.11 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 6.57(s, 2H)5.83 (s, 1H), 5.76 (s, 1H), 5.55 (s, 1H), 3.58 (s, 3H), 3.53 - 3.41 (m, 2H), 3.44 - 3.30 (m, 2H), 2.96 (s, 1H), 2.39 - 2.04 (m, 2H), 1.97 (d, J = 1.3 Hz, 3H), 1.87 (s, 2H), 1.67 (d, J = 5.8 Hz, 2H), 1.60 (d, J = 6.5 H, 4H), 1.49(s, 4H).	513.30

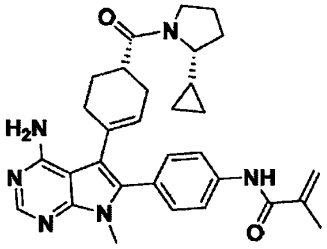
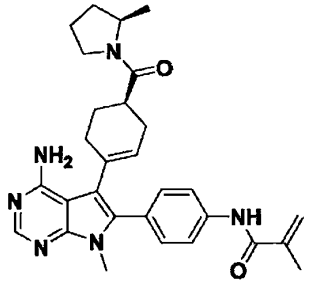
[1232]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-((R)-4-((R)-2-甲基哌啶-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.09 (s, 1H), 7.87 - 7.75 (m, 2H), 7.51 - 7.29 (m, 2H), 6.57 (s, 2H), 5.83 (t, J = 1.1 Hz, 1H), 5.76 (t, J = 1.9 Hz, 1H), 5.55 (s, 1H), 4.77 (s, 1H), 4.28 - 3.67 (m, 1H), 3.58 (s, 3H), 3.15 - 2.58 (m, 2H), 2.42 - 2.11 (m, 2H), 1.97 (d, J = 1.2 Hz, 3H), 1.80 (d, J = 13.6 Hz, 2H), 1.68 - 1.41 (m, 7H), 1.11 (dd, J = 78.3, 6.8 Hz, 4H).	513.30
N-(4-(5-((R)-4-((1S,5R)-2-氮杂双环[3.1.0]己烷-2-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.10 (d, J = 1.0 Hz, 1H), 7.91 - 7.64 (m, 2H), 7.44 (dq, J = 8.7, 2.1, 1.5 Hz, 2H), 6.71 - 6.31 (m, 1H), 5.83 (s, 1H), 5.77 (d, J = 3.6 Hz, 1H), 5.56 (t, J = 1.4 Hz, 1H), 3.72 - 3.61 (m, 1H), 3.59 (d, J = 0.9 Hz, 3H), 3.49 (d, J = 5.9 Hz, 1H), 3.18 - 2.64 (m, 2H), 2.45 - 2.19 (m, 2H), 2.19 - 1.77 (m, 8H), 1.69 (dd, J = 13.2, 6.6 Hz, 2H), 1.55 (dd, J = 28.9, 6.9 Hz, 1H), 0.88 - 0.73 (m, 1H), 0.63 - 0.51 (m, 1H).	497.25
N-(4-(5-((S)-4-((1R,5S)-2-氮杂双环[3.1.0]己烷-2-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.10 (d, J = 1.0 Hz, 1H), 7.89 - 7.72 (m, 2H), 7.53 - 7.32 (m, 2H), 6.52 (s, 1H), 5.84 (d, J = 1.3 Hz, 1H), 5.77 (s, 1H), 5.56 (d, J = 1.9 Hz, 1H), 3.75 - 3.63 (m, 1H), 3.59 (d, J = 0.9 Hz, 3H), 3.49 (q, J = 6.5, 5.8 Hz, 1H), 3.22 - 2.63 (m, 2H), 2.41 - 2.14 (m, 2H), 2.13 - 2.01 (m, 1H), 2.00 - 1.97(m, 3H), 1.96 - 1.81 (d, J = 6.3 Hz, 2H), 1.75-1.63(m, 2H), 1.61- 1.45 (m, 1H), 0.86 - 0.77 (m, 1H), 0.62 - 0.48 (m, 1H).	497.30

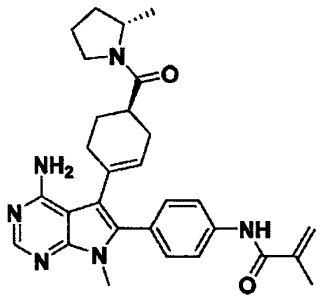
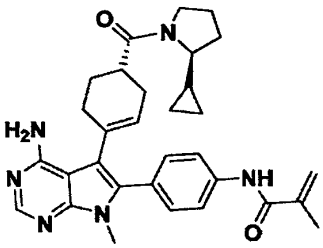
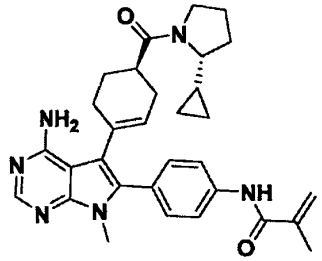
[1233]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-((R)-4-((1R,5S)-2-氮杂双环[3.1.0]己烷-2-羰基)环己-1-烯-1-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.10 (s, 1H), 7.81 (dt, J = 8.8, 2.1 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 6.54 (s, 1H), 5.83 (s, 1H), 5.77 (d, J = 9.8 Hz, 1H), 5.55 (s, 1H), 3.80 - 3.65 (m, 1H), 3.58 (s, 4H), 3.23 - 3.07 (m, 1H), 2.96 - 2.63 (m, 1H), 2.32 (q, J = 18.6, 18.0 Hz, 2H), 1.98 (m, 4H), 1.94 - 1.74 (m, 3H), 1.67 (ddd, J = 21.7, 11.2, 5.8 Hz, 2H), 0.77 (q, J = 7.4, 6.7 Hz, 1H), 0.69 (q, J = 6.7 Hz, 0H), 0.59 - 0.43 (m, 1H).	497.25
N-(4-(4-氨基-7-甲基-5-((S)-4-((R)-2-甲基吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.09 (d, J = 4.8 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.47 - 7.39 (m, 2H), 6.59 (s, 2H), 5.83 (s, 1H), 5.77 (s, 1H), 5.55 (s, 1H), 4.03 (q, J = 9.6, 8.8 Hz, 1H), 3.58 (d, J = 2.2 Hz, 3H), 3.48 (q, J = 7.3, 6.4 Hz, 1H), 3.32 (s, 1H), 2.82 (s, 1H), 2.32 (d, J = 17.2 Hz, 1H), 2.20 (d, J = 17.1 Hz, 1H), 1.97 (s, 3H), 1.96 - 1.73 (m, 5H), 1.61 (s, 2H), 1.47 (s, 1H), 1.14 (d, J = 6.4 Hz, 1H), 1.04 (d, J = 6.3 Hz, 2H).	499.25
N-(4-(4-氨基-7-甲基-5-((S)-4-((S)-2-甲基吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.10 (d, J = 4.7 Hz, 1H), 7.84 - 7.77 (m, 2H), 7.43 (dd, J = 8.7, 2.1 Hz, 2H), 6.62 (s, 2H), 5.83 (s, 1H), 5.76 (d, J = 3.8 Hz, 1H), 5.55 (d, J = 1.9 Hz, 1H), 4.10 - 3.97 (m, 1H), 3.58 (d, J = 2.2 Hz, 3H), 3.48 (q, J = 6.8, 6.2 Hz, 1H), 2.83 (q, J = 5.4 Hz, 1H), 2.32 (d, J = 16.7 Hz, 1H), 2.20 (d, J = 18.7 Hz, 1H), 2.00 - 1.86 (m, 4H), 1.84 (s, 3H), 1.66 - 1.57 (m, 2H), 1.52 - 1.41 (m, 2H), 1.14 (d, J = 6.3 Hz, 1H), 1.05 (d, J = 6.2 Hz, 3H).	499.30

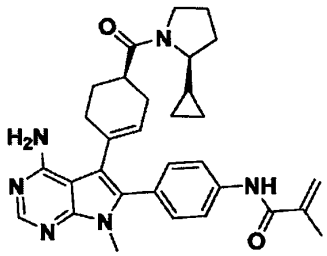
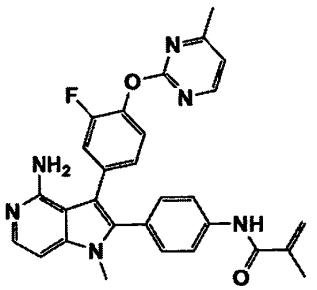
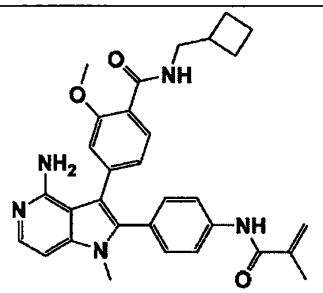
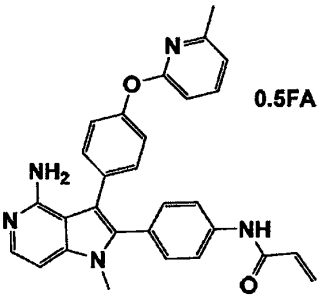
[1234]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-((S)-4-((R)-2-环丙基吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) 9.93 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.83 -7.77 (m, 2H), 7.43 (dd, J = 8.7, 2.7 Hz, 2H), 6.63-6.45 (m, 2H), 5.83 (t, J = 2.9 Hz, 1H), 5.77 (s, 1H), 5.57-5.52 (m, 1H), 3.80 (t, J=7.5Hz,1H),3.60-3.50(s,3H),3.50-3.40(s,2H),2.86(s,1H),2.40-2.10(m,2H),2.00-1.95(s,3H),1.95-1.65(m,6H), 1.65-1.50(s,2H),1.00-0.75(m,1H), 0.53 -0.41 (m, 1H), 0.32-0.13 (m, 2H), 0.10 (dt, J = 9.8, 4.3 Hz, 1H).(m,2H),2.00-1.95(s,3H),1.95-1.65(m,6H),1.65-1.50(s,2H), 1.00-0.75(m,1H), 0.53 - 0.41 (m, 1H), 0.32 - 0.13 (m, 2H), 0.10 (dt, J = 9.8, 4.3 Hz, 1H).	525.25
N-(4-(4-氨基-7-甲基-5-((R)-4-((R)-2-甲基吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.10 (d, J = 3.7 Hz, 1H), 7.81 (dd, J = 8.3, 3.9 Hz, 2H), 7.43 (dd, J = 8.7, 2.5 Hz, 2H), 6.46 (s, 2H), 5.83 (s, 1H), 5.75 (s, 1H), 5.55 (s, 1H), 4.05 - 3.96 (m, 1H), 3.58 (d, J = 1.9 Hz, 4H), 3.46 - 3.39 (m, 1H), 2.77 (s, 1H), 2.27 - 2.22 (m, 2H), 1.94 (d, J = 22.2 Hz, 8H), 1.60 (s, 2H), 1.49 (d, J = 7.6 Hz, 1H), 1.09 (dd, J = 8.2, 6.2 Hz, 3H).	499.30

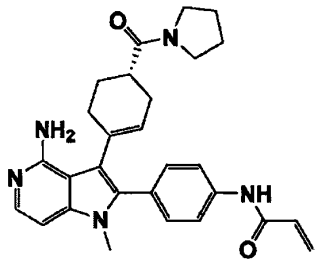
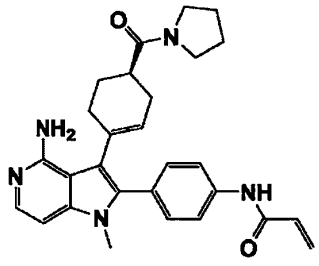
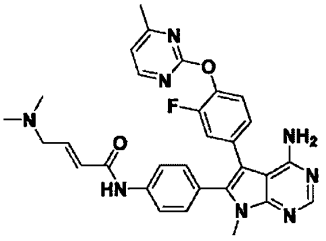
[1235]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-((R)-4-((S)-2-甲基吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 3.8 Hz, 1H), 7.81 (dq, J = 9.1, 2.1 Hz, 2H), 7.43 (dd, J = 8.8, 2.5 Hz, 2H), 6.46 (s, 2H), 5.83 (s, 1H), 5.79 - 5.72 (m, 1H), 5.55 (d, J = 1.9 Hz, 1H), 4.01 (td, J = 6.6, 2.7 Hz, 1H), 3.58 (d, J = 1.9 Hz, 3H), 3.44 (t, J = 7.9 Hz, 1H), 2.76 (dd, J = 12.2, 6.3 Hz, 1H), 2.25 (s, 2H), 1.97 (t, J = 1.2 Hz, 4H), 1.90 (s, 3H), 1.81 (s, 2H), 1.61 (s, 2H), 1.52 - 1.45 (m, 1H), 1.09 (dd, J = 8.2, 6.3 Hz, 3H).	499.30
N-(4-(4-氨基-5-((S)-4-((S)-2-环丙基吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) 9.94 (s, 1H), 8.11 (d, J = 2.6 Hz, 1H), 7.81 (dd, J = 8.5, 5.9 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.44 (s, 1H), 5.83 (s, 1H), 5.79 - 5.73 (m, 1H), 5.55 (t, J = 1.5 Hz, 1H), 3.75 (t, J = 7.0 Hz, 1H), 3.58 (d, J = 1.8 Hz, 3H), 3.55 (s, 1H), 3.55 - 3.42 (m, 1H),2.78 (s, 1H),2.27 (s, 1H), 2.22 (s, 1H), 1.97 (d, J = 1.3 Hz, 9H),1.79(d, J = 1.3 Hz, 3H) 0.91 (d, J = 7.8 Hz, 1H), 0.50 (dd, J = 9.6, 4.9 Hz, 1H), 0.35 (dddt, J = 27.8, 13.4, 9.3, 4.6 Hz, 2H), 0.13 (dt, J = 9.5, 4.8 Hz, 1H).	525.25
N-(4-(4-氨基-5-((R)-4-((R)-2-环丙基吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.95 (s, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.85 - 7.73 (m, 2H), 7.45 - 4.41 (m, 2H), 6.65 (s, 2H), 5.82 (d, J = 4.9 Hz, 1H), 5.77 (s, 1H), 5.55 (d, J = 1.8 Hz, 1H), 3.81 - 3.79 (m, 1H), 3.58 (s, 5H), 2.86 (s, 1H), 2.42 -2.14 (m, 2H), 1.97 (d, J = 1.3 Hz, 2H), 1.88 - 1.67 (m, 4H), 1.67 - 1.55 (m, 2H), 0.87 - 0.85 (m, 1H), 0.47 (d, J = 4.3 Hz, 1H), 0.38 - 0.14 (m, 2H), 0.09 (d, J = 4.8 Hz, 1H).	525.30

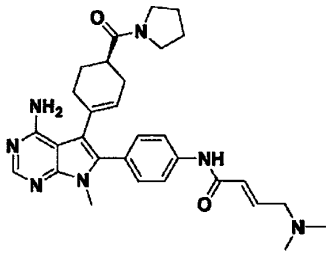
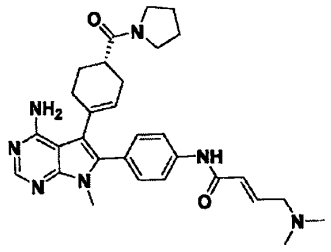
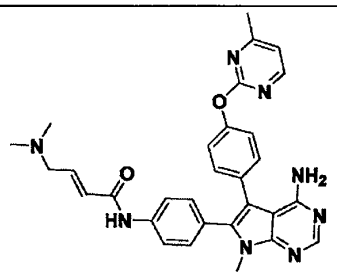
[1236]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-((R)-4-((S)-2-环丙基吡咯烷-1-羰基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 9.95 (s, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.87 - 7.75 (m, 2H), 7.43 (d, J = 8.3 Hz, 2H), 6.44 (s, 2H), 5.83 (s, 1H), 5.76 (s, 1H), 5.55 (d, J = 1.8 Hz, 1H), 3.74 (t, J = 7.2 Hz, 1H), 3.58 (d, J = 2.1 Hz, 4H), 3.46 - 3.40 (m, 1H), 2.79 (d, J = 7.2 Hz, 1H), 2.24 (d, J = 20.6 Hz, 2H), 2.02 - 1.88 (m, 6H), 1.89 - 1.50 (m, 5H), 0.95 - 0.86 (m, 1H), 0.55 - 0.25 (m, 3H), 0.15 - 0.11 (m, 1H).	525.30
N-(4-(4-氨基-3-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-1-甲基-1H-吡咯并[3,2-c]吡啶-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 7.78 - 7.69 (m, 3H), 7.37 - 7.27 (m, 3H), 7.24 - 7.16 (m, 2H), 7.16 - 7.09 (m, 1H), 6.88 (d, J = 6.0 Hz, 1H), 5.80 (s, 1H), 5.54 (s, 1H), 5.15 (s, 2H), 3.57 (s, 3H), 2.42 (s, 3H), 1.96 (s, 3H).	509.20
4-(4-氨基-2-(4-甲基丙烯酰胺基苯基)-1-甲基-1H-吡咯并[3,2-c]吡啶-3-基)-N-(环丁基甲基)-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.10 (t, J = 5.8 Hz, 1H), 7.75 - 7.66 (m, 3H), 7.64 (d, J = 7.8 Hz, 1H), 7.31 - 7.23 (m, 2H), 6.95 (d, J = 1.6 Hz, 1H), 6.91 - 6.84 (m, 2H), 5.80 (t, J = 1.2 Hz, 1H), 5.53 (t, J = 1.6 Hz, 1H), 5.18 (s, 2H), 3.73 (s, 3H), 3.57 (s, 3H), 3.29 (m, J = 12.0 Hz, 2H), 2.54 (d, J = 7.6 Hz, 1H), 2.04 - 1.92 (m, 5H), 1.89 - 1.78 (m, 2H), 1.78 - 1.65 (m, 2H).	524.25
N-(4-(4-氨基-1-甲基-3-(4-((6-甲基吡啶-2-基)氧基)苯基)-1H-吡咯并[3,2-c]吡啶-2-基)苯基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.80 - 7.62 (m, 4H), 7.34 - 7.23 (m, 4H), 7.11 - 7.06 (m, 2H), 7.02 (d, J = 7.4 Hz, 1H), 6.99 (s, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.48-6.41 (m, 1H), 6.29-6.25 (m, 1H), 5.79-5.76 (m, 1H), 5.52 (s, 2H), 3.62 (s, 3H), 2.35 (s, 4H).	476.20

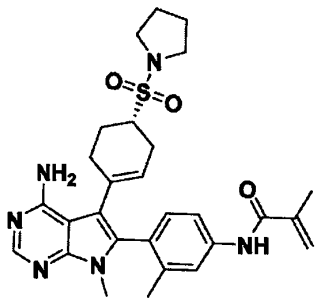
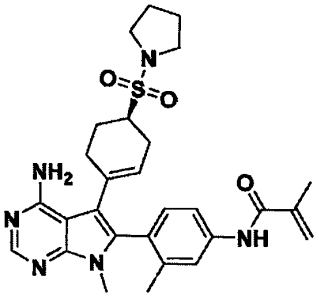
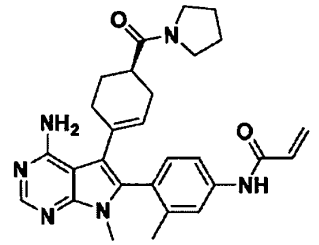
[1237]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-1-甲基-3-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-1H-吡咯并[3,2-c]吡啶-2-基)苯基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.30 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 5.9 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 6.2 Hz, 1H), 6.51-6.44 (m, 1H), 6.32-6.27 (m, 1H), 5.83 - 5.74 (m, 2H), 5.69 (s, 2H), 3.55 (d, J = 1.9 Hz, 3H), 3.52 - 3.41 (m, 1H), 3.30 - 3.22 (m, 2H), 2.79 - 2.64 (m, 1H), 2.38 - 2.16 (m, 2H), 2.04 - 1.82 (m, 4H), 1.76 (p, J = 6.6 Hz, 2H), 1.61 (d, J = 30.7 Hz, 2H).	470.20
(R)-N-(4-(4-氨基-1-甲基-3-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-1H-吡咯并[3,2-c]吡啶-2-基)苯基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.30 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 5.9 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 6.2 Hz, 1H), 6.51-6.44 (m, 1H), 6.32-6.27 (m, 1H), 5.83 - 5.74 (m, 2H), 5.69 (s, 2H), 3.55 (d, J = 1.9 Hz, 3H), 3.52 - 3.41 (m, 1H), 3.30 - 3.22 (m, 2H), 2.79 - 2.64 (m, 1H), 2.38 - 2.16 (m, 2H), 2.04 - 1.82 (m, 4H), 1.76 (p, J = 6.6 Hz, 2H), 1.61 (d, J = 30.7 Hz, 2H).	470.25
(E)-N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-(二甲基氨基)丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.4 Hz, 3H), 7.23 - 7.15 (m, 2H), 7.15 - 7.07 (m, 1H), 6.76 (dt, J = 15.1, 5.9 Hz, 1H), 6.29 (d, J = 15.4 Hz, 1H), 5.98 (s, 2H), 3.60 (s, 3H), 3.12 (d, J = 5.9 Hz, 2H), 2.42 (s, 3H), 2.22 (s, 6H).	553.25

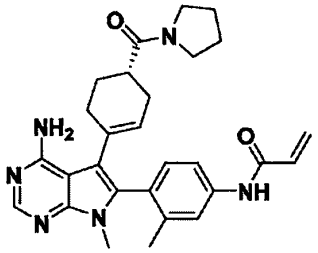
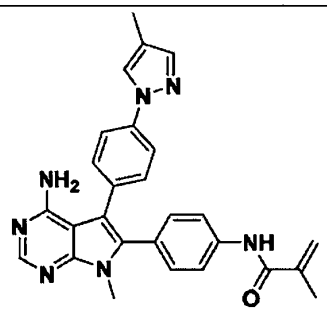
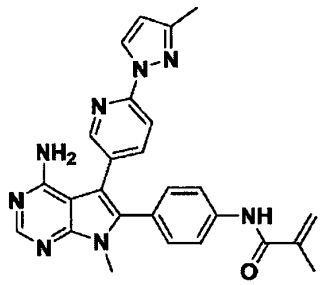
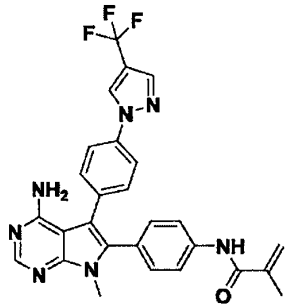
[1238]

化合物	结构	质子 NMR	MS [M+1]
(R,E)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-(二甲基氨基)丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.51 - 7.38 (m, 2H), 6.77 (dt, J = 15.3, 5.9 Hz, 1H), 6.53 (s, 2H), 6.32 (d, J = 15.4 Hz, 1H), 5.84 - 5.72 (m, 1H), 3.58 (s, 3H), 3.56 - 3.47 (m, 1H), 3.47 - 3.39 (m, 1H), 3.27 (dd, J = 16.0, 9.3 Hz, 3H), 3.11 (d, J = 5.9 Hz, 2H), 2.84 (q, J = 6.0 Hz, 1H), 2.27 (d, J = 14.7 Hz, 2H), 2.22 (s, 6H), 1.87 (dt, J = 13.3, 6.4 Hz, 4H), 1.76 (p, J = 6.7 Hz, 2H), 1.63 (q, J = 6.4 Hz, 2H).	528.40
(S,E)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-(二甲基氨基)丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.10 (d, J = 1.7 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.47 - 7.40 (m, 2H), 6.77 (dt, J = 15.4, 5.9 Hz, 1H), 6.53 (s, 2H), 6.31 (d, J = 15.3 Hz, 1H), 5.76 (d, J = 4.5 Hz, 1H), 3.58 (d, J = 1.8 Hz, 3H), 3.56 - 3.48 (m, 1H), 3.47 - 3.38 (m, 1H), 3.32 - 3.21 (m, 1H), 3.10 (d, J = 5.8 Hz, 2H), 2.83 (p, J = 6.0 Hz, 1H), 2.40 - 2.23 (m, 2H), 2.21 (s, 6H), 1.87 (dt, J = 13.2, 6.4 Hz, 4H), 1.76 (p, J = 6.5 Hz, 2H), 1.63 (d, J = 6.3 Hz, 2H).	528.35
(E)-N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-(二甲基氨基)丁-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.74 - 7.67 (m, 2H), 7.36 - 7.24 (m, 4H), 7.23 - 7.07 (m, 4H), 6.75 (dt, J = 15.4, 5.8 Hz, 1H), 6.28 (dt, J = 15.4, 1.6 Hz, 1H), 5.90 (s, 2H), 3.60 (s, 3H), 3.07 (dd, J = 5.9, 1.6 Hz, 2H), 2.41 (s, 3H), 2.19 (s, 7H).	535.35

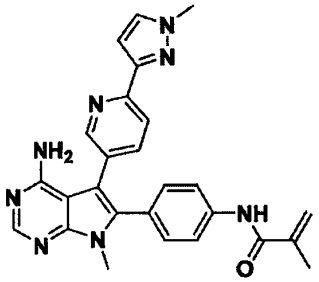
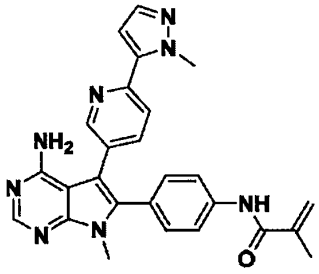
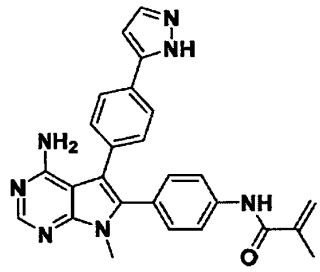
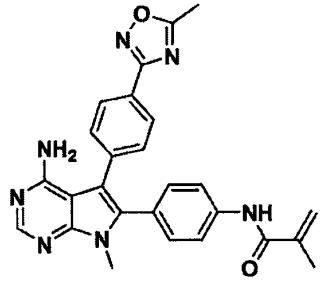
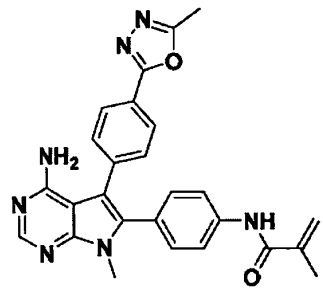
[1239]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-基磺酰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.12 (s, 1H), 7.72 (dd, J = 13.0, 2.2 Hz, 1H), 7.63 (ddd, J = 13.1, 8.3, 2.2 Hz, 1H), 7.18 (dd, J = 12.5, 8.3 Hz, 1H), 6.35 (s, 2H), 5.83 (t, J = 1.1 Hz, 1H), 5.62 (s, 1H), 5.59 - 5.50 (m, 1H), 3.54 (d, J = 15.4 Hz, 1H), 3.34 (s, 3H), 3.31 - 3.24 (m, 4H), 2.37 (d, J = 30.0 Hz, 2H), 2.10 - 2.02 (m, 5H), 1.97 (t, J = 1.3 Hz, 3H), 1.95 - 1.79 (m, 5H), 1.56 (p, J = 10.8 Hz, 1H).	535.25
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-基磺酰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.40 (s, 1H), 7.78 (d, J = 2.1 Hz, 3H), 7.20 (dd, J = 9.9, 8.3 Hz, 1H), 5.84 (s, 1H), 5.71 (s, 1H), 5.56 (d, J = 1.9 Hz, 1H), 3.43 (d, J = 1.6 Hz, 4H), 3.31 - 3.23 (m, 4H), 2.42 (s, 2H), 2.06 (d, J = 3.6 Hz, 4H), 1.97 (t, J = 1.2 Hz, 4H), 1.94 - 1.82 (m, 5H), 1.60 (s, 1H).	535.25
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) 10.24 (d, J = 1.5 Hz, 1H), 8.10 (s, 1H), 7.78 -7.64 (m, 1H), 7.59 (ddd, J = 7.9, 5.5, 2.1 Hz, 1H), 7.20 (dd, J = 8.3, 6.5 Hz, 1H), 6.47 (dd, J = 17.0, 10.1 Hz,2H), 6.29 (dd, J = 16.9, 2.0 Hz, 1H), 5.79 (dd, J = 10.1, 2.1 Hz, 1H), 5.67 (d, J = 15.5 Hz, 1H), 3.53 -3.37 (m, 2H), 3.34 (s, 3H), 3.27 (q, J = 6.9 Hz, 2H), 2.73 (p, J = 6.2 Hz, 1H), 2.21 (q, J = 18.5 Hz, 2H), 1.93 (d, J = 14.5 Hz, 3H), 1.89 -1.80 (m, 4H), 1.80 -1.68 (m, 2H), 1.57 (d, J = 6.3 Hz, 2H).	485.15

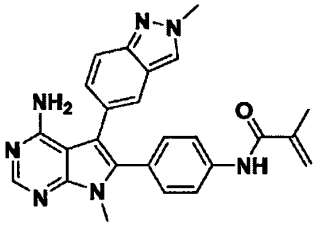
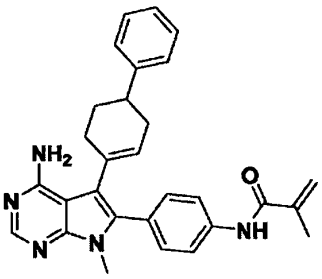
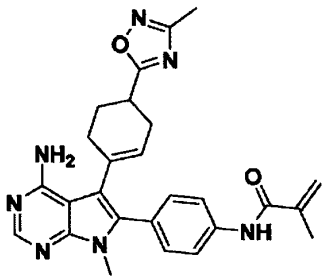
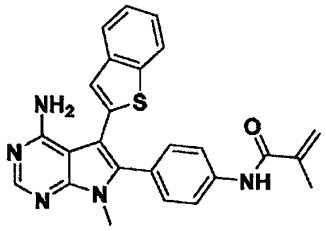
[1240]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) 10.24 (d, J = 1.5 Hz, 1H), 8.10 (s, 1H), 7.78 -7.64 (m, 1H), 7.59 (ddd, J = 7.9, 5.5, 2.1 Hz, 1H), 7.20 (dd, J = 8.3, 6.5 Hz, 1H), 6.47 (dd, J = 17.0, 10.1 Hz,2H), 6.29 (dd, J = 16.9, 2.0 Hz, 1H), 5.79 (dd, J = 10.1, 2.1 Hz, 1H), 5.67 (d, J = 15.5 Hz, 1H), 3.53 -3.37 (m, 2H), 3.34 (s, 3H), 3.27 (q, J = 6.9 Hz, 2H), 2.73 (p, J = 6.2 Hz, 1H), 2.21 (q, J = 18.5 Hz, 2H), 1.93 (d, J = 14.5 Hz, 3H), 1.89 -1.80 (m, 4H), 1.80 -1.68 (m, 2H), 1.57 (d, J = 6.3 Hz, 2H).	485.15
N-(4-(4-氨基-7-甲基-5-(4-(4-甲基-1H-吡唑-1-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 7.79-7.66 (m, 4H), 7.56 (s, 1H), 7.34-7.25 (m, 4H), 5.89 (s, 2H), 5.79 (t, J = 1.0 Hz, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.62 (s, 3H), 2.10 (s, 3H), 1.94 (t, J = 1.2 Hz, 3H).	464.10
N-(4-(4-氨基-7-甲基-5-(6-(3-甲基-1H-吡唑-1-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.47 (d, J = 2.5 Hz, 1H), 8.25 - 8.15 (m, 2H), 7.80 (dd, J = 8.4, 0.8 Hz, 1H), 7.77 - 7.68 (m, 3H), 7.33 - 7.25 (m, 2H), 6.37 (d, J = 2.5 Hz, 1H), 6.09 (s, 2H), 5.82 - 5.77 (m, 1H), 5.55 - 5.50 (m, 1H), 3.62 (s, 3H), 2.29 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	465.30
N-(4-(4-氨基-7-甲基-5-(4-(4-(三氟甲基)-1H-吡唑-1-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.20 - 9.15 (m, 1H), 8.21 (d, J = 1.2 Hz, 2H), 7.91 - 7.83 (m, 2H), 7.75 - 7.68 (m, 2H), 7.41 - 7.34 (m, 2H), 7.33 - 7.25 (m, 2H), 5.95 (s, 2H), 5.81 - 5.76 (m, 1H), 5.56 - 5.50 (m, 1H), 3.62 (s, 3H), 1.95 (t, J = 1.3 Hz, 3H).	518.30

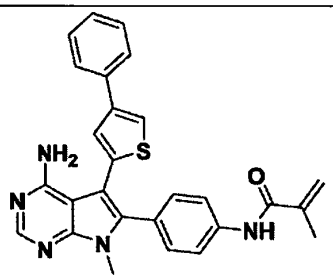
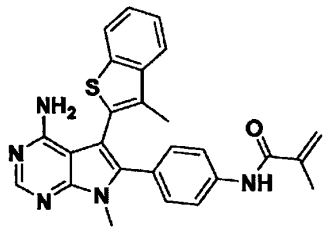
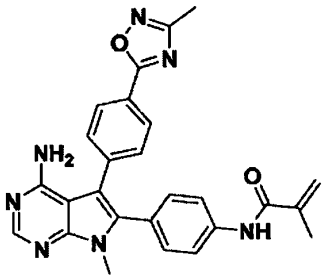
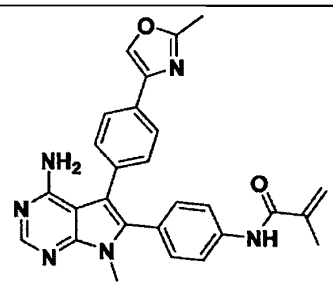
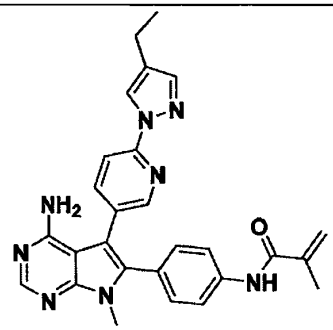
[1241]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(6-(1-甲基-1H-吡唑-3-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.35 - 8.30 (m, 1H), 8.22 (s, 1H), 7.85 (dd, J = 8.2, 0.9 Hz, 1H), 7.79 - 7.69 (m, 3H), 7.63 (dd, J = 8.2, 2.3 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 6.77 (d; J = 2.2 Hz, 1H), 6.02 (s, 1H), 5.79 (s, 1H), 5.53 (s, 1H), 3.91 (s, 3H), 3.62 (s, 3H), 1.94 (t, J = 1.3 Hz, 3H).	465.20
N-(4-(4-氨基-7-甲基-5-(6-(1-甲基-1H-吡唑-5-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.44 (dd, J = 2.3, 0.9 Hz, 1H), 8.23 (s, 1H), 7.81 - 7.70 (m, 3H), 7.69 (dd, J = 8.2, 2.3 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 - 7.28 (m, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.10 (s, 2H), 5.80 (t, J = 1.1 Hz, 1H), 5.54 (t, J = 1.4 Hz, 1H), 4.14 (s, 3H), 3.62 (s, 3H), 1.95 (t, J = 1.2 Hz, 3H).	460.30
N-(4-(5-(4-(1H-吡唑-5-基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (1H, s), 9.88 (1H, s), 8.21 (1H, s), 7.84-7.62 (5H, m), 7.32-8211;7.23 (4H, m), 6.72 (1H, d, J=2.2 Hz), 5.79 (3H, s), 5.52 (1H, t, J=1.5 Hz), 3.63 (3H, s), 1.95 (3H, d, J=1.2 Hz)	450.30
N-(4-(4-氨基-7-甲基-5-(4-(5-甲基-1,2,4-恶二唑-3-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.22 (s, 1H), 7.94 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.96 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.62 (s, 3H), 3.31 (s, 1H), 2.66 (s, 3H), 1.95 (s, 3H).	466.35
N-(4-(4-氨基-7-甲基-5-(4-(5-甲基-1,3,4-恶二唑-2-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.22 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 5.99 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.62 (s, 3H), 3.32 (s, 1H), 2.57 (s, 3H), 1.95 (s, 3H).	466.20

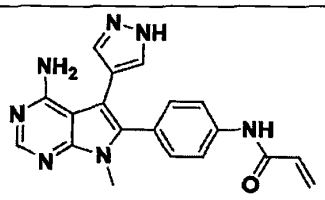
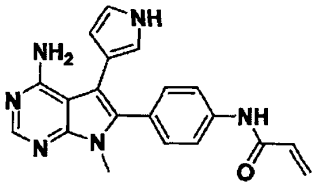
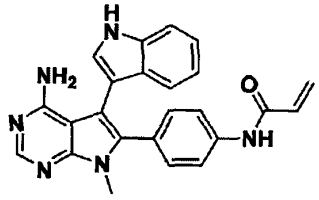
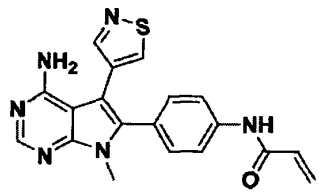
[1242]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(2-甲基-2H-吲唑-5-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.29 (s, 1H), 8.19 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 9.2 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.07 (dd, J = 8.8, 1.8 Hz, 1H), 5.77 (s, 1H), 5.52 (s, 1H), 4.15 (s, 3H), 3.64 (s, 3H), 1.93 (s, 3H).	438.15
N-(4-(4-氨基-7-甲基-5-(1,2,3,6-四氢-[1,1'-联苯]-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.14 (s, 1H), 7.88-7.80 (m, 2H), 7.50- 7.42 (m, 2H), 7.34-7.23 (m, 4H), 7.23-7.14 (m, 1H), 6.29 (s, 1H), 5.89-5.82 (m, 2H), 5.56 (t, J = 1.4 Hz, 1H), 3.58 (s, 3H), 2.82 (dd, J = 10.7, 5.7 Hz, 1H), 2.42 (d, J = 17.3 Hz, 1H), 2.28 (d, J = 16.6 Hz, 1H), 2.14 (s, 1H), 1.98 (t, J = 1.2 Hz, 3H), 1.92 (d, J = 4.8 Hz, 1H), 1.77 (s, 2H).	464.30
N-(4-(4-氨基-7-甲基-5-(4-(3-甲基-1,2,4-恶二唑-5-基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.12 (s, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 5.82 (d, J = 8.1 Hz, 2H), 5.55 (s, 1H), 3.58 (s, 3H), 3.45 (s, 1H), 2.69-2.57 (m, 2H), 2.33 (s, 3H), 1.98 (s, 3H), 1.95-1.76 (m, 4H).	470.25
N-(4-(4-氨基-5-(苯并[b]噻吩-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.23 (s, 1H), 7.85 (dd, J = 18.2, 7.7 Hz, 2H), 7.76-7.69 (m, 2H), 7.42-7.32 (m, 4H), 7.32 (td, J = 7.5, 1.5 Hz, 1H), 6.22 (s, 2H), 5.79 (s, 1H), 5.53 (s, 1H), 3.62 (s, 3H), 1.94 (d, J = 1.2 Hz, 3H).	440.10

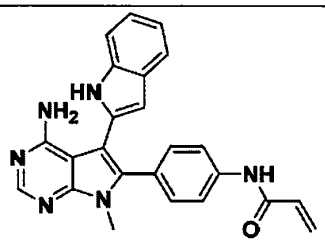
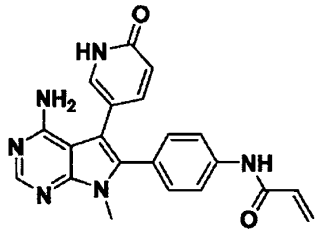
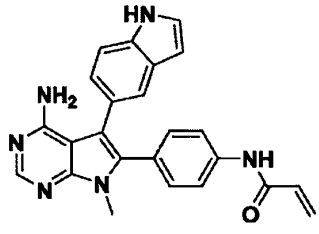
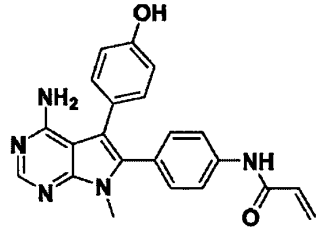
[1243]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-苯基噻吩-2-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.22 (s, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.76 (dd, J = 8.5, 2.5 Hz, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 1.6 Hz, 1H), 7.41 (dt, J = 7.9, 3.3 Hz, 4H), 7.30 (t, J = 7.4 Hz, 1H), 6.13 (s, 2H), 5.80 (s, 1H), 5.53 (s, 1H), 3.61 (s, 3H), 1.95 (s, 3H).	466.20
N-(4-(4-氨基-7-甲基-5-(3-甲基苯并[b]噻吩-2-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.22 (s, 1H), 7.94-7.86 (m, 1H), 7.79-7.70 (m, 1H), 7.70-7.59 (m, 2H), 7.46-7.35 (m, 2H), 7.35-7.26 (m, 2H), 5.76 (t, J = 1.1 Hz, 1H), 5.55-5.46 (m, 1H), 3.68 (s, 3H), 2.07 (s, 3H), 1.92 (t, J = 1.3 Hz, 3H).	454.05
N-(4-(4-氨基-7-甲基-5-(4-(3-甲基-1,2,4-恶二唑-5-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.23 (s, 1H), 8.07 - 7.99 (m, 2H), 7.76 - 7.68 (m, 2H), 7.46 - 7.38 (m, 2H), 7.32 - 7.24 (m, 2H), 6.02 (s, 2H), 5.80 (t, J = 1.1 Hz, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.62 (s, 3H), 2.41 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H).	466.25
N-(4-(4-氨基-7-甲基-5-(4-(2-甲基恶唑-4-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.39 (s, 1H), 7.81 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 8.5 Hz, 3H), 7.33 -7.22 (m, 3H), 5.81 (s, 1H), 5.50 (s, 1H), 5.10 (s, 2H), 3.75 (s, 3H), 2.53 (s, 3H), 2.08 (s, 3H),1.91 (s, 1H).	465.30
N-(4-(4-氨基-5-(6-(4-乙基-1H-吡唑-1-基)吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.42 (s, 1H), 8.30 (ddd, J = 4.7, 2.1, 0.9 Hz, 2H), 7.92 (dd, J = 8.5, 0.8 Hz, 1H), 7.70 (dd, J = 8.5, 2.3 Hz, 1H), 7.66 -.56 (m, 4H), 7.29 -7.21 (m, 2H), 5.82 (s, 1H), 5.52 (d, J = 1.7 Hz, 1H), 5.01 (s, 2H), 3.76 (s, 3H), 2.59 (q, J = 7.5 Hz, 2H), 2.09 (dd, J = 1.6, 0.9 Hz, 3H), 1.27 (t, J = 7.6 Hz, 3H).	479.35

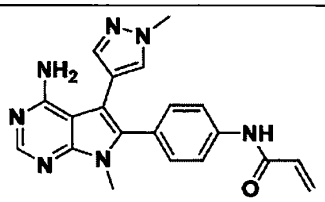
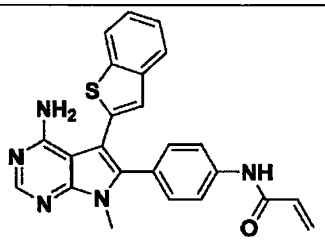
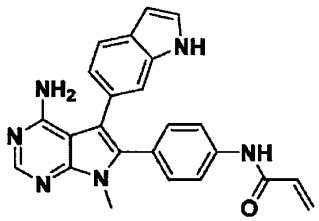
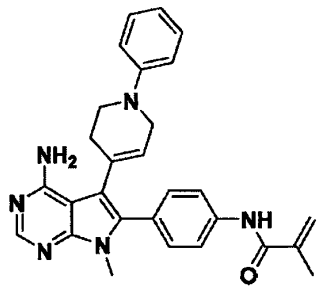
[1244]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 10.28 (s, 1H), 8.17 (d, J = 1.3 Hz, 1H), 7.54 (dd, J = 143.2, 8.2 Hz, 6H), 6.46 (dd, J = 16.9, 10.0 Hz, 1H), 6.29 (dt, J = 16.9, 1.7 Hz, 1H), 5.94 (s, 2H), 5.79 (d, J = 10.2 Hz, 1H), 3.58 (s, 3H).	360.10
N-(4-(4-氨基-7-甲基-5-(1H-吡咯-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 10.24 (s, 1H), 8.13 (s, 1H), 7.72 - 7.65 (m, 2H), 7.40 - 7.32 (m, 2H), 6.79 (q, J = 2.4 Hz, 1H), 6.65 (q, J = 2.0 Hz, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 5.99 (q, J = 2.4 Hz, 1H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.56 (s, 3H).	359.15
N-(4-(4-氨基-5-(1H-吲哚-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24-11.19 (m, 1H), 10.19 (s, 1H), 8.17 (s, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.36- 7.27 (m, 3H), 7.18 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.41 (dd, J = 16.9, 10.1 Hz, 1H), 6.24 (dd, J = 16.9, 2.1 Hz, 1H), 5.75 (dd, J = 10.0, 2.1 Hz, 2H), 3.66 (s, 3H).	409.15
N-(4-(4-氨基-5-(异噻唑-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.87 (s, 1H), 8.28 (s, 1H), 8.21 (s, 1H), 7.75-7.68 (m, 2H), 7.35-7.28 (m, 2H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 6.01 (s, 1H), 5.79 (dd, J = 10.1, 2.1 Hz, 1H), 3.60 (s, 3H).	377.10

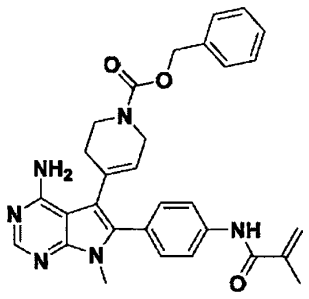
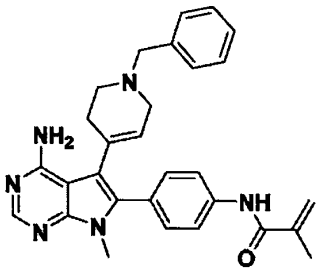
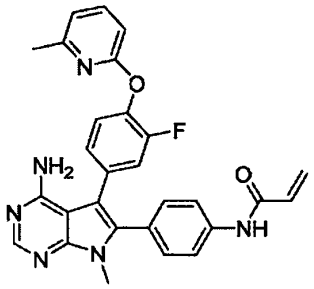
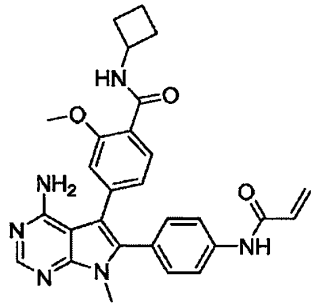
[1245]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(1H-吲哚-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 10.25 (s, 1H), 8.22 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.11-7.03 (m, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.55-6.21 (m, 3H), 6.10 (s, 2H), 5.77 (dd, J = 10.0, 2.0 Hz, 1H), 3.66 (s, 3H).	409.10
N-(4-(4-氨基-7-甲基-5-(6-侧氧基-1,6-二氢吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 10.28 (s, 1H), 8.17 (s, 1H), 7.77- 7.71 (m, 2H), 7.37-7.25 (m, 2H), 7.21 (dd, J = 9.4, 2.6 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 6.46 (dd, J = 17.0, 10.1 Hz, 1H), 6.33-6.25 (m, 2H), 6.12 (s, 2H), 5.79 (dd, J = 10.1, 2.0 Hz, 1H), 3.58 (s, 3H).	387.15
N-(4-(4-氨基-5-(1H-吲哚-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 10.20 (s, 1H), 8.17 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 1.6 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.96 (dd, J = 8.3, 1.7 Hz, 1H), 6.47-6.36 (m, 2H), 6.25 (dd, J = 16.9, 2.1 Hz, 1H), 5.76 (dd, J = 10.0, 2.1 Hz, 1H), 3.63 (s, 3H).	409.15
N-(4-(4-氨基-5-(4-羟基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 9.49 (s, 1H), 8.16 (s, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.31-7.24 (m, 2H), 7.08-7.00 (m, 2H), 6.78-6.71 (m, 2H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.60 (s, 3H).	386.15

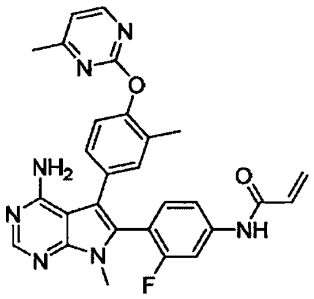
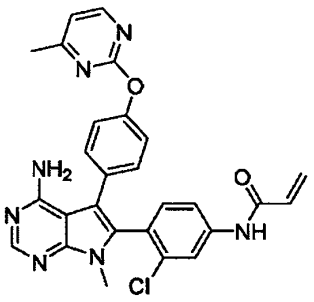
[1246]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(1-甲基-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.16 (s, 1H), 7.84 -7.59 (m, 3H), 7.39-7.31 (m, 2H), 7.27 (d, J = 0.9 Hz, 1H), 6.46 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 6.01 (s, 2H), 5.79 (dd, J = 10.1, 2.1 Hz, 1H), 3.81 (s, 3H), 3.56 (s, 3H).	374.10
N-(4-(4-氨基-5-(苯并[b]噻吩-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.23 (s, 1H), 7.90-7.79 (m, 2H), 7.75-7.67 (m, 2H), 7.45-7.37 (m, 2H), 7.41-7.32 (m, 2H), 7.32 (ddd, J = 8.5, 7.1, 1.5 Hz, 1H), 6.43 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.0 Hz, 2H), 5.77 (dd, J = 10.1, 2.1 Hz, 1H), 3.62 (s, 3H).	426.10
N-(4-(4-氨基-5-(1H-吲哚-6-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (t, J = 2.3 Hz, 1H), 10.21 (s, 1H), 8.18 (s, 1H), 7.67-7.60 (m, 2H), 7.53 (d, J = 8.1 Hz, 1H), 7.36-7.26 (m, 3H), 7.23 (q, J = 1.0 Hz, 1H), 6.91 (dd, J = 8.1, 1.5 Hz, 1H), 6.47 – 6.36 (m, 2H), 6.25 (dd, J = 17.0, 2.1 Hz, 1H), 5.76 (dd, J = 10.0, 2.1 Hz, 2H), 3.63 (s, 3H).	409.15
N-(4-(4-氨基-7-甲基-5-(1-苯基-1,2,3,6-四氢吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.15 (s, 1H), 7.80 (d, J = 7.9 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.20 (t, J = 7.7 Hz, 2H), 6.91 (d, J = 8.2 Hz, 2H), 6.73 (t, J = 7.2 Hz, 1H), 6.26 (s, 2H), 5.92 (s, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 3.84 (s, 2H), 3.58 (s, 3H), 2.16-2.05 (m, 4H), 1.97 (s, 3H).	465.25

[1247]

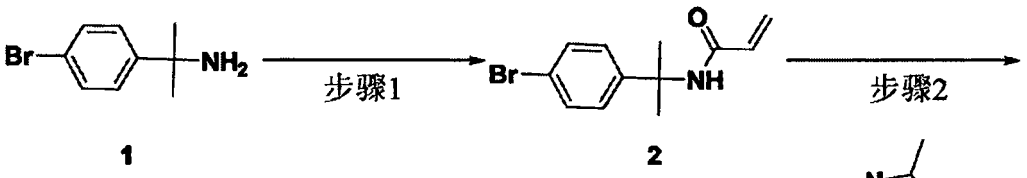
化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(4-甲基丙烯酰胺基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-3,6-二氢吡啶-1(2H)-甲酸苯甲酯		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.14 (s, 1H), 7.83 (dd, J = 8.7, 2.3 Hz, 2H), 7.53-7.27 (m, 7H), 6.33 (s, 2H), 5.80 (d, J = 21.2 Hz, 2H), 5.55 (s, 1H), 5.09 (s, 2H), 4.06 (s, 2H), 3.56 (s, 3H), 3.46 (s, 2H), 1.99 (d, J = 11.6 Hz, 5H).	523.20
N-(4-(4-氨基-5-(1-苯甲基-1,2,3,6-四氢吡啶-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.14 (s, 1H), 7.87-7.80 (m, 2H), 7.47-7.40 (m, 2H), 7.33 (d, J = 5.1 Hz, 4H), 7.27 (s, 1H), 6.26 (s, 2H), 5.81 (d, J = 25.0 Hz, 2H), 5.56 (t, J = 1.5 Hz, 1H), 3.56 (s, 5H), 3.34 (s, 2H), 3.10 (s, 2H), 1.98 (d, J = 1.3 Hz, 5H).	479.25
N-(4-(4-氨基-5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.21 (s, 1H), 7.81 - 7.67 (m, 3H), 7.37 - 7.29 (m, 2H), 7.26 (t, J = 8.4 Hz, 1H), 7.16 (dd, J = 11.5, 2.0 Hz, 1H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.62 (s, 3H), 2.30 (s, 3H).	495.20
4-(6-(4-乙酰胺基苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环丁基-2-甲氧基苯甲酰胺		^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.22 (d, J = 3.3 Hz, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 6.95 - 6.81 (m, 2H), 6.45 (dd, J = 17.0, 9.9 Hz, 1H), 6.28 (dd, J = 17.0, 2.2 Hz, 1H), 5.79 (dd, J = 9.9, 2.2 Hz, 1H), 4.39 (q, J = 8.3 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 2.21 (s, 2H), 1.98 (q, J = 9.7 Hz, 2H), 1.76 - 1.53 (m, 2H).	497.20

[1248]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(3-甲基-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.43 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.81 (dd, J = 12.1, 2.0 Hz, 1H), 7.44 - 7.27 (m, 2H), 7.22 (s, 1H), 7.15 - 7.02 (m, 3H), 6.44 (dd, J = 17.0, 10.0 Hz, 1H), 6.31 (dd, J = 17.0, 2.1 Hz, 1H), 5.82 (dd, J = 10.0, 2.0 Hz, 1H), 3.53 (s, 3H), 2.41 (s, 3H), 2.03 (s, 3H).	510.15
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氯苯基)丙烯酰胺		^{1}H NMR (300 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.57 (dd, J = 8.4, 2.1 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.20 - 7.05 (m, 3H), 6.50 - 6.25 (m, 2H), 5.83 (dd, J = 9.8, 2.3 Hz, 1H), 3.48 (s, 3H), 2.40 (s, 3H).	512.10

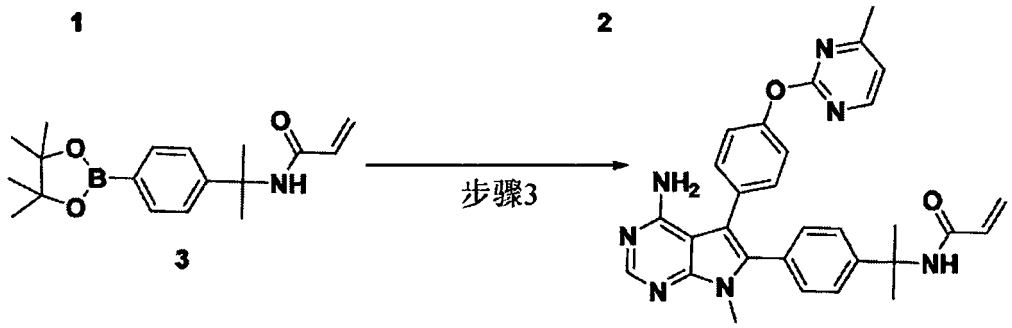
[1249] 实例13

[1250] 流程11



1 2

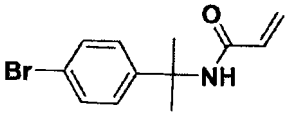
[1251]



3

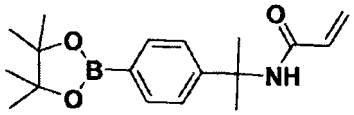
[1252] N-(2-(4-溴苯基)丙-2-基)丙烯酰胺

[1253]



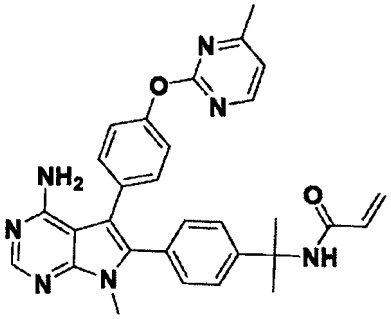
[1254] 步骤1:在氮气气氛下,在0℃下,将丙烯酰氯(0.63g,7.006mmol)分数份逐滴添加至2-(4-溴苯基)丙-2-胺(1.50g,7.006mmol)及TEA(2.13g,21.018mmol)于DCM(30mL)中的经搅拌溶液/混合物中。在0℃下搅拌混合物1小时。所得混合物用CH_2Cl_2萃取。合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,在减压下浓缩滤液,得到呈黄色固体状的N-(2-(4-溴苯基)丙-2-基)丙烯酰胺(500mg,27%)。

[1255] N-(2-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)丙-2-基)丙烯酰胺

[1256] 

[1257] 步骤2:N-[2-(4-溴苯基)丙-2-基]丙-2-烯酰胺(470.00mg,1.753mmol)、双(频哪醇根基)二硼(667.63mg,2.629mmol)、AcOK(516.05mg,5.258mmol)及Pd(dppf)Cl2(128.25mg,0.175mmol)于DMF(10mL)中的溶液/混合物在氮气气氛下,在80℃下搅拌2小时。所得混合物用EtOAc萃取。合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,在减压下浓缩滤液。残余物用PE/EtOAc=4/1洗脱、通过硅胶柱色谱来纯化,得到呈灰白色固体状的N-(2-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)丙-2-基)丙烯酰胺(400mg,72%)。

[1258] N-(2-(4-(4-氨基-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙-2-基)丙烯酰胺

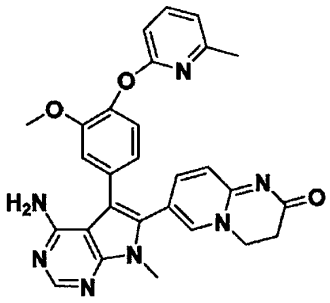
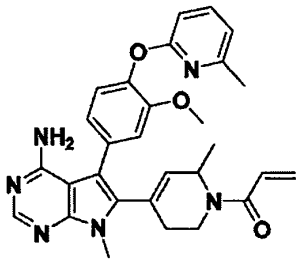
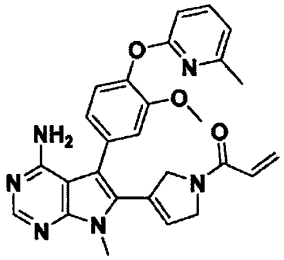
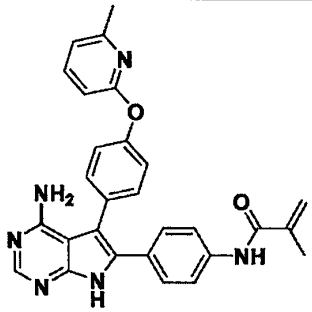
[1259] 

[1260] 步骤3:6-碘-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-4-胺(200.00mg,0.44mmol)、N-[2-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]丙-2-基]丙-2-烯酰胺(165.1mg,0.52mmol)、K_3PO_4(277.9mg,1.31mmol)及Pd(dppf)Cl_2(31.9mg,0.04mmol)于DMF(4mL)及H_2O(1mL)中的溶液/混合物在氮气气氛下、在90℃下搅拌1小时。所得混合物用EtOAc萃取。合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,在减压下浓缩滤液。粗产物通过HPLC纯化(柱:XBridge ShieldRP18 OBD柱,5um,19*150mm;移动相A:水(10mM NH_4HCO_3),移动相B:ACN;流量:25mL/min;梯度:25B至43B,历时7分钟;220/254nm;RT1:6.25;RT2:;注射体积:ml;操作次数:;)。冻干产生呈灰白色无定形固体状的N-(2-(4-(4-氨基-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙-2-基)丙烯酰胺(51mg,22.3%)。

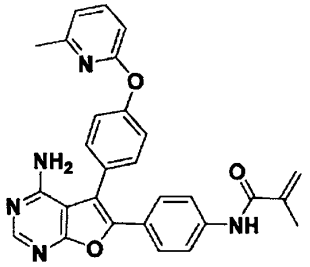
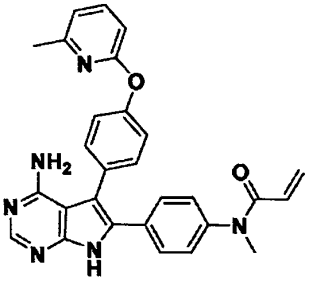
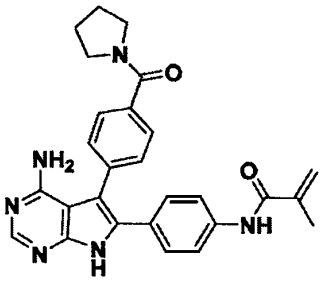
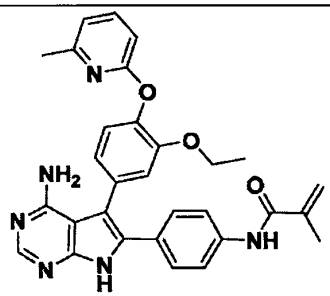
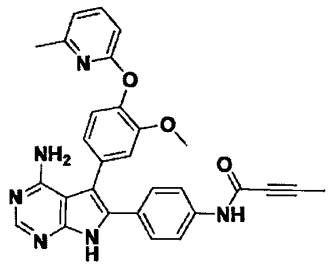
[1261] 根据实例13的方法制备的其它化合物描绘于下表12中。

[1262] 表12.其它示例性化合物

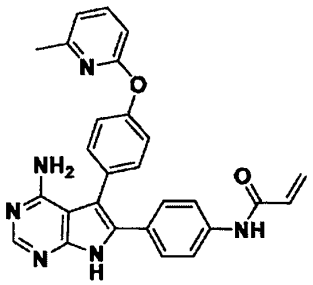
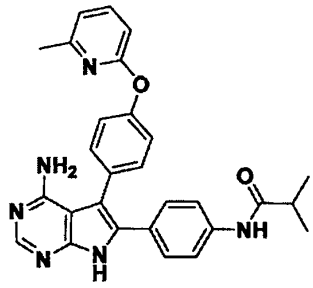
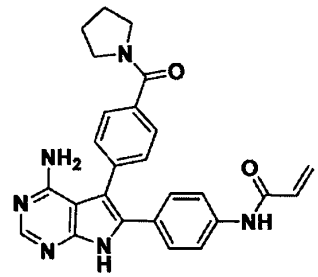
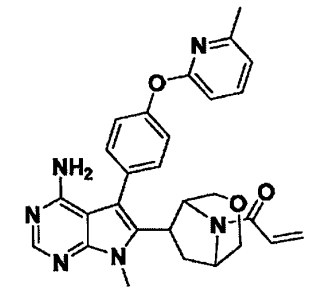
[1263]

化合物	结构	质子 NMR	MS [M+1]
7-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,4-二氢吡啶并[1,2-a]嘧啶-2-酮		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.41 (s, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.53 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.20 - 7.13 (m, 2H), 7.05 (d, *J* = 9.2 Hz, 1H), 6.94 - 6.84 (m, 3H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.20 (s, 2H), 4.20 (t, *J* = 7.4 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H).	508.00
1-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-6-甲基-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.67 (td, *J* = 7.7, 2.1 Hz, 1H), 7.18 (dd, *J* = 8.0, 6.2 Hz, 1H), 7.10 - 7.05 (m, 1H), 7.00 - 6.92 (m, 2H), 6.86 - 6.73 (m, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.09 (dt, *J* = 34.3, 19.4 Hz, 2H), 5.86 (s, 1H), 5.67 (d, *J* = 11.0 Hz, 1H), 4.93 - 4.61 (m, 1H), 4.48 (s, 1H), 4.14 - 3.73 (m, 1H), 3.67 (s, 6H), 3.25 - 2.64 (m, 1H), 2.30 (d, *J* = 3.1 Hz, 3H), 1.96 (dd, *J* = 67.9, 16.5 Hz, 1H), 1.31 - 0.80 (m, 3H).	511.40
1-(3-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.67 (td, *J* = 7.7, 4.7 Hz, 1H), 7.25 - 7.12 (m, 2H), 7.04 - 6.90 (m, 2H), 6.68 (dd, *J* = 8.2, 3.6 Hz, 1H), 6.58 (dd, *J* = 16.7, 10.3 Hz, 1H), 6.42 - 6.10 (m, 3H), 6.02(s, 1H), 5.68 (ddd, *J* = 16.3, 10.2, 2.4 Hz, 1H), 4.56 (p, *J* = 2.5 Hz, 1H), 4.33 (s, 2H), 4.05 (p, *J* = 2.2 Hz, 1H), 3.79 (d, *J* = 2.9 Hz, 3H), 3.69 (s, 3H), 2.30 (d, *J* = 11.6 Hz, 3H).	483.20
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 9.83 (s, 1H), 8.12 (s, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.65 - 7.57 (m, 2H), 7.42 - 7.35 (m, 2H), 7.38 - 7.26 (m, 2H), 7.23 - 7.15 (m, 2H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 5.78 (s, 2H), 5.52 (t, *J* = 1.5 Hz, 1H), 2.38 (s, 3H), 1.94 (d, *J* = 1.3 Hz, 3H).	477.30

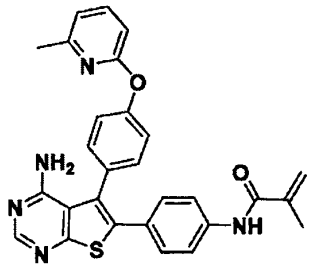
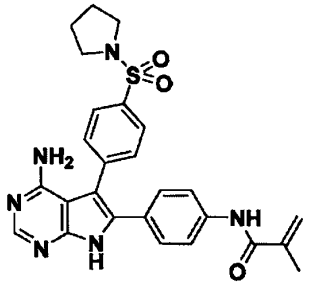
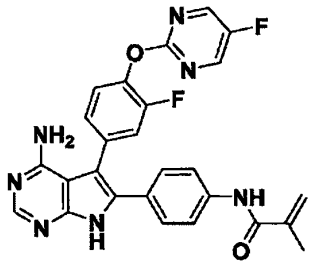
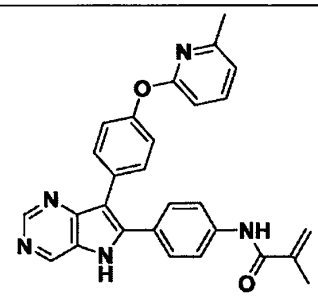
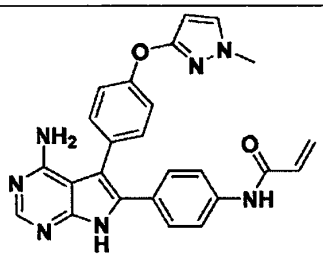
[1264]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)呋喃并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.27 (s, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.75 (t, J = 7.8 Hz, 1H), 7.50 (dd, J = 8.4, 5.2 Hz, 4H), 7.11 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 5.84 (s, 1H), 5.56 (s, 1H), 2.33 (s, 3H), 1.98 (s, 3H).	478.30
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-N-甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ12.17 (s, 1H), 8.14 (s, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.44 (dd, J = 15.1, 8.2 Hz, 4H), 7.23 (dd, J = 8.2, 5.9 Hz, 4H), 7.04 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.24 - 5.44 (m, 5H), 3.24 (s, 3H), 2.37 (s, 3H).	477.35
N-(4-(4-氨基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 9.82 (s, 1H), 8.13 (s, 1H), 7.59 (d, J = 8.3 Hz, 4H), 7.39 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 5.79 (s, 1H), 5.52 (s, 1H), 3.48 (dt, J = 11.2, 6.4 Hz, 4H), 1.94 (s, 3H), 1.87 (dq, J = 13.0, 6.8 Hz, 4H).	467.30
N-(4-(4-氨基-5-(3-乙氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 12.05 (s, 1H), 9.83 (s, 1H), 8.13 (s, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.66 - 7.60 (m, 2H), 7.39 - 7.30 (m, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 1.9 Hz, 1H), 7.01 - 6.90 (m, 2H), 6.74 (d, J = 8.2 Hz, 1H), 5.79 (s, 2H), 5.53 (t, J = 1.5 Hz, 1H), 3.91 (q, J = 6.9 Hz, 2H), 2.34 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H), 1.27 - 1.07 (m, 1H), 1.00 (t, J = 6.9 Hz, 3H).	521.25
N-(4-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丁-2-炔酰胺		1H NMR (400 MHz, DMSO-d6) δ 12.07 (s, 1H), 10.66 (s, 1H), 8.13 (s, 1H), 7.74 - 7.65 (m, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.38 - 7.29 (m, 2H), 7.21 - 7.06 (m, 2H), 7.02 - 6.88 (m, 2H), 6.72 (d, J = 8.2 Hz, 1H), 5.84 (s, 1H), 3.62 (s, 2H), 2.34 (s, 3H), 2.05 (s, 2H).	505.25

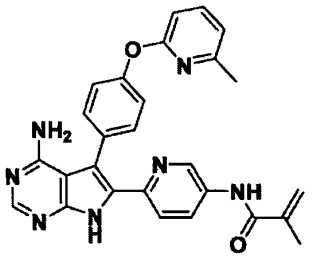
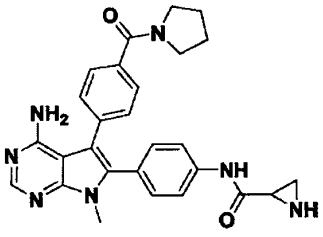
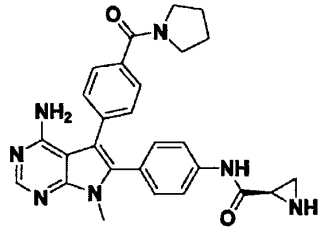
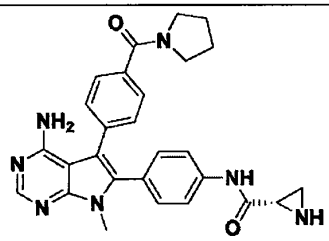
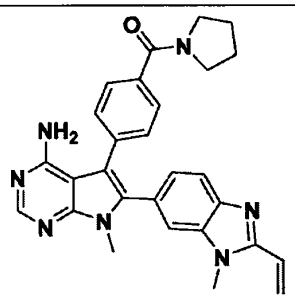
[1265]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 10.19 (s, 1H), 8.12 (s, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.41 - 7.36 (m, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.22 - 7.16 (m, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.43 (dd, J = 17.0, 10.1 Hz, 1H), 6.26 (dd, J = 17.0, 2.0 Hz, 1H), 5.76 (dd, J = 10.1, 2.0 Hz,2H), 2.38 (s, 3H).	463.40
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)异丁酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.87 (s, 1H), 8.12 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.39 - 7.35 (m, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.75 (s, 1H), 2.79 - 2.57 (m, 1H), 2.38 (s, 3H), 1.09 (d, J = 6.8 Hz, 6H).	479.45
N-(4-(4-氨基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 10.20 (s, 1H), 8.13 (s, 1H), 7.62 - 7.54 (m, 4H), 7.45 - 7.36 (m, 2H), 7.31 - 7.23 (m, 2H), 6.42 (dd, J = 17.0, 10.1 Hz, 1H), 6.25 (dd, J = 17.0, 2.1 Hz, 1H), 5.76 (dd, J = 10.0, 2.1 Hz, 2H), 3.54 - 3.43 (m, 4H), 2.08 (s, 1H), 1.88 (dt, J = 12.6, 6.7 Hz, 4H).	453.30
1-(6-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氧杂-8-氮杂双环[3.2.1]辛-8-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 3.2 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.45 - 7.09 (m, 4H), 7.05 (d, J = 7.4 Hz, 1H), 6.87 (dd, J = 10.3, 8.2 Hz, 1H), 6.65 (ddd, J = 35.0, 16.7, 10.3 Hz, 1H), 6.24 (ddd, J = 16.7, 4.8, 2.4 Hz, 1H), 5.70 (td, J = 10.5, 2.4 Hz, 1H), 4.68 (s, 1H), 4.50 (d, J = 16.1 Hz, 2H), 3.95 (dt, J = 24.1, 7.3 Hz, 1H), 3.77 - 3.67 (m, 5H), 3.67 - 3.52 (m, 2H), 3.44 (dd, J = 10.8, 6.1 Hz, 1H), 2.37 (d, J = 2.4 Hz, 3H), 2.31 - 2.06 (m, 2H).	497.35

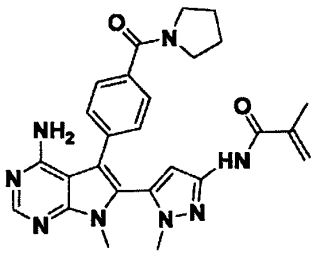
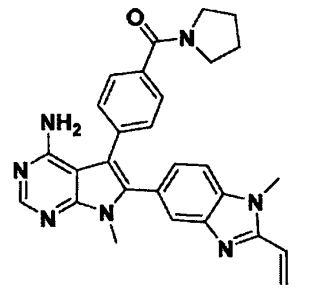
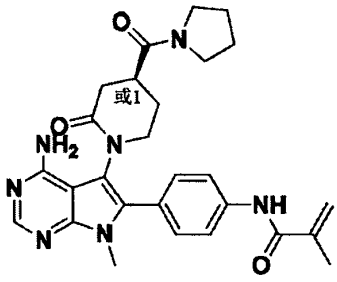
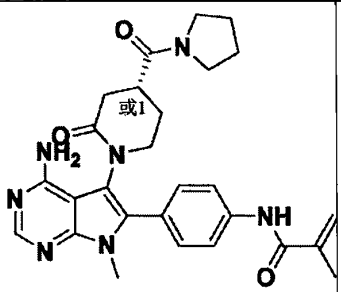
[1266]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)噻吩并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.35 (s, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.74 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.03 (t, J = 7.6 Hz, 3H), 6.79 (d, J = 8.1 Hz, 1H), 5.83 (s, 1H), 5.56 (s, 1H), 2.33 (s, 3H), 1.97 (s, 3H).	494.30
N-(4-(4-氨基-5-(4-(吡咯烷-1-基磺酰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 12.21 (s, 1H), 9.85 (s, 1H), 8.14 (s, 1H), 7.88 - 7.81 (m, 2H), 7.62 - 7.52 (m, 4H), 7.16 (d, J = 8.8 Hz, 2H), 5.86 (s, 2H), 5.78 (s, 1H), 5.52 (s, 1H), 3.24 - 3.12 (m, 2H), 1.94 (d, J = 1.2 Hz, 3H), 1.71 - 1.63 (m, 3H), 1.57 (s, 1H), 1.32 (q, J = 7.2 Hz, 1H), 0.94 (t, J = 7.2 Hz, 1H).	503.2
N-(4-(4-氨基-5-(3-氟-4-((5-氟嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 9.85 (s, 1H), 8.81 (s, 2H), 8.14 (s, 1H), 7.70 - 7.59 (m, 2H), 7.48 (t, J = 8.4 Hz, 1H), 7.38 - 7.26 (m, 3H), 7.24 (dd, J = 8.3, 2.0 Hz, 1H), 5.80 (s, 3H), 5.53 (d, J = 1.7 Hz, 1H), 1.95 (s, 3H).	500.35
N-(4-(7-(4-((6-甲基吡啶-2-基)氧基)苯基)-5H-吡咯并[3,2-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 12.24 (s, 1H), 9.99 (s, 1H), 8.91 (s, 1H), 8.86 (s, 1H), 7.83 - 7.76 (m, 2H), 7.75 (t, J = 7.8 Hz, 1H), 7.58 - 7.50 (m, 4H), 7.17 - 7.10 (m, 2H), 7.02 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.83 (s, 1H), 5.56 (s, 1H), 2.36 (s, 3H), 1.97 (d, J = 1.2 Hz, 3H).	462.3
N-(4-(4-氨基-5-(4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.13 (s, 1H), 8.12 (d, J = 13.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.59 - 7.52 (m, 2H), 7.46 - 7.39 (m, 2H), 7.23 - 7.14 (m, 3H), 6.57 - 6.37 (m, 1H), 6.24 (m, J = 17.0, 2.1 Hz, 1H), 5.96 (s, 2H), 5.81 - 5.69 (m, 1H), 3.80 (s, 3H).	452

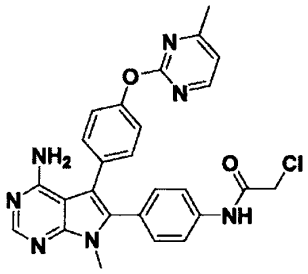
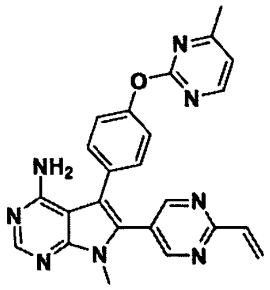
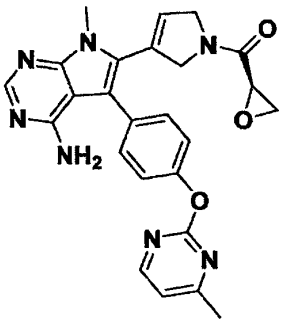
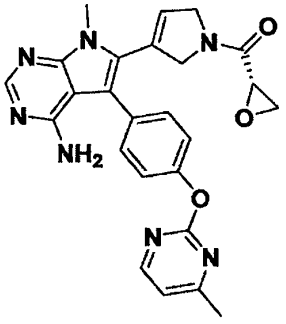
[1267]

化合物	结构	质子 NMR	MS [M+1]
N-(6-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 10.04 (s, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.13 (s, 1H), 7.91 (dd, J = 8.8, 2.5 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.28 - 7.20 (m, 2H), 7.07 (t, J = 7.6 Hz, 2H), 6.88 (d, J = 8.1 Hz, 1H), 5.85 (s, 2H), 5.58 (s, 1H), 2.39 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	478.30
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)氮丙啶-2-甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.55 - 7.49 (m, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.40 - 7.29 (m, 4H), 4.33 (dd, J = 5.6, 2.6 Hz, 1H), 3.99 (t, J = 5.8 Hz, 1H), 3.69 (s, 3H), 3.61 (t, J = 6.9 Hz, 2H), 3.50 (t, J = 6.6 Hz, 2H), 3.45 (dd, J = 6.0, 2.7 Hz, 1H), 1.97 (dq, J = 25.9, 6.8 Hz, 4H).	482.20
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)氮丙啶-2-甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.55 - 7.49 (m, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.40 - 7.29 (m, 4H), 4.33 (dd, J = 5.6, 2.6 Hz, 1H), 3.99 (t, J = 5.8 Hz, 1H), 3.69 (s, 3H), 3.61 (t, J = 6.9 Hz, 2H), 3.50 (t, J = 6.6 Hz, 2H), 3.45 (dd, J = 6.0, 2.7 Hz, 1H), 1.97 (dq, J = 25.9, 6.8 Hz, 4H).	482.20
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)氮丙啶-2-甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.22 (s, 1H), 7.55 - 7.49 (m, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.40 - 7.29 (m, 4H), 4.33 (dd, J = 5.6, 2.6 Hz, 1H), 3.99 (t, J = 5.8 Hz, 1H), 3.69 (s, 3H), 3.61 (t, J = 6.9 Hz, 2H), 3.50 (t, J = 6.6 Hz, 2H), 3.45 (dd, J = 6.0, 2.7 Hz, 1H), 1.97 (dq, J = 25.9, 6.8 Hz, 4H).	482.20
(4-(4-氨基-7-甲基-6-(1-甲基-2-乙烯基-1H-苯并[d]咪唑-6-基)-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.48 - 7.42 (m, 2H), 7.31 - 7.25 (m, 2H), 7.12 - 7.05 (m, 1H), 7.04 (dd, J = 16.1, 10.0 Hz, 1H), 6.43 (dd, J = 17.1, 2.1 Hz, 1H), 5.94 (s, 1H), 5.73 (dd, J = 11.0, 2.0 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.41 (dt, J = 24.1, 6.5 Hz, 4H), 1.82 (dq, J = 19.1, 6.8 Hz, 4H).	478.25

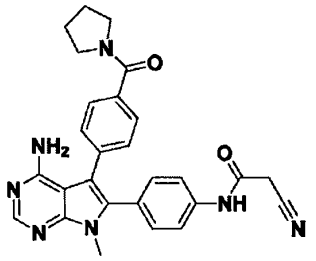
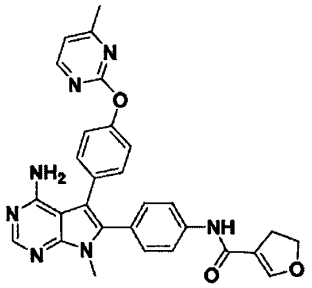
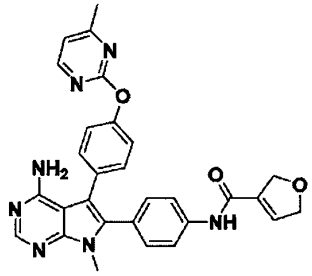
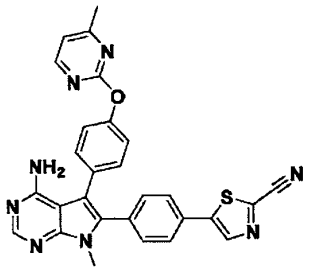
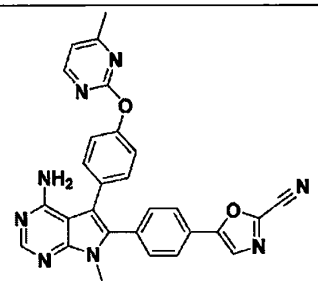
[1268]

化合物	结构	质子 NMR	MS [M+1]
(S)-N-(5-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.43 (s, 1H), 8.13 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.05 (s, 1H), 5.89 (s, 1H), 5.53 (d, *J* = 1.8 Hz, 1H), 5.20 (s, 2H), 3.74 (s, 3H), 3.68 (t, *J* = 6.9 Hz, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.25 (s, 3H), 2.09 (s, 3H), 1.97 (dp, *J* = 24.7, 6.7 Hz, 4H).	485.20
(4-(4-氨基-7-甲基-6-(1-甲基-2-乙烯基-1H-苯并[d]咪唑-5-基)-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.62 - 7.53 (m, 2H), 7.48 - 7.41 (m, 2H), 7.30 - 7.23 (m, 2H), 7.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.04 (dd, *J* = 17.1, 11.0 Hz, 1H), 6.41 (dd, *J* = 17.1, 2.1 Hz, 1H), 5.92 (s, 2H), 5.72 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.85 (s, 3H), 3.61 (s, 3H), 3.41 (dt, *J* = 18.5, 6.5 Hz, 4H), 1.81 (dq, *J* = 20.2, 6.8 Hz, 4H).	478.25
(S)-N-(4-(4-氨基-7-甲基-5-(2-侧氧基-4-(吡咯烷-1-羰基)哌啶-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.10 (s, 1H), 7.88 - 7.80 (m, 2H), 7.42 - 7.33 (m, 2H), 6.91 (s, 2H), 5.83 (t, *J* = 1.1 Hz, 1H), 5.59 - 5.53 (m, 1H), 3.62 (s, 3H), 3.53 (dt, *J* = 10.2, 6.6 Hz, 1H), 3.45 - 3.33 (m, 2H), 3.32 - 3.29 (m, 1H), 3.15 (s, 1H), 2.95 (dd, *J* = 11.4, 4.9 Hz, 1H), 2.49 - 2.32 (m, 2H), 1.98 (d, *J* = 1.2 Hz, 4H), 1.88 (p, *J* = 6.2 Hz, 2H), 1.79 (p, *J* = 7.8, 7.1 Hz, 2H), 1.68 (s, 1H), 1.24 (s, 1H).	502.25
(R)-N-(4-(4-氨基-7-甲基-5-(2-侧氧基-4-(吡咯烷-1-羰基)哌啶-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.10 (s, 1H), 7.88 - 7.80 (m, 2H), 7.43 - 7.33 (m, 2H), 6.93 (s, 1H), 5.83 (t, *J* = 1.0 Hz, 1H), 5.59 - 5.53 (m, 1H), 3.62 (s, 3H), 3.53 (dt, *J* = 10.3, 6.6 Hz, 1H), 3.45 - 3.33 (m, 2H), 3.32 (s, 1H), 3.15 (s, 1H), 2.99 - 2.91 (m, 1H), 2.47 - 2.33 (m, 2H), 1.98 (d, *J* = 1.2 Hz, 4H), 1.88 (d, *J* = 6.6 Hz, 2H), 1.80 (d, *J* = 6.5 Hz, 2H), 1.73 - 1.61 (m, 1H), 1.24 (s, 1H).	502.25

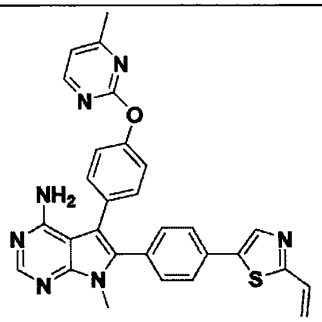
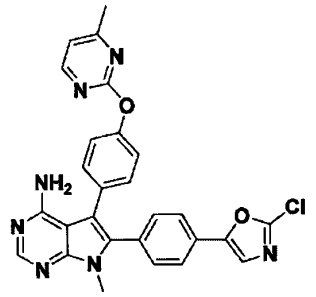
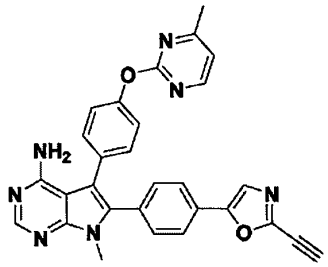
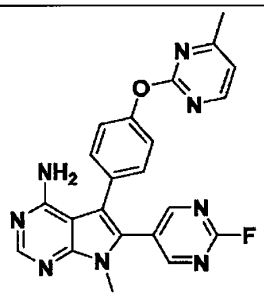
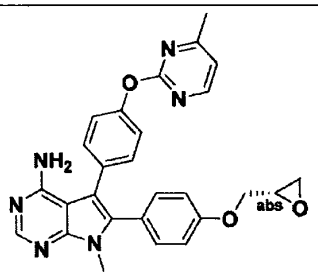
[1269]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-氯乙酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.41 (d, J = 5.1 Hz, 1H), 8.21 (s, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 9.3 Hz, 4H), 7.24 - 7.06 (m, 3H), 4.21 (s, 2H), 3.71 (s, 3H), 2.50 (s, 3H).	500.30
7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-6-(2-乙烯基嘧啶-5-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.66 (s, 2H), 8.44 - 8.36 (m, 2H), 7.40-7.30 (m, 2H), 7.38-7.23 (m, 2H), 6.98 - 6.86 (m, 2H), 6.68 (dd, J = 17.4, 1.7 Hz, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.16 (s, 2H), 3.81 (s, 3H), 2.53 (s, 3H).	437.25
(R)-(3-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基)(环氧乙烷-2-基)甲酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.44 (dd, J = 5.1, 3.5 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.58 - 7.48 (m, 2H), 7.38 - 7.27 (m, 2H), 7.16 (dd, J = 5.1, 2.3 Hz, 1H), 6.25 (dt, J = 23.2, 2.0 Hz, 1H), 4.82 - 4.61 (m, 1H), 4.49 - 4.29 (m, 2H), 4.20 (d, J = 3.9 Hz, 1H), 3.87 (d, J = 13.1 Hz, 3H), 3.60 (ddd, J = 90.2, 4.3, 2.4 Hz, 1H), 2.94 (ddd, J = 36.6, 6.4, 4.3 Hz, 1H), 2.81 (ddd, J = 28.6, 6.4, 2.4 Hz, 1H), 2.52 (d, J = 2.1 Hz, 3H).	470.20
(S)-(3-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基)(环氧乙烷-2-基)甲酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.44 (dd, J = 5.1, 3.5 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.58 - 7.48 (m, 2H), 7.38 - 7.27 (m, 2H), 7.16 (dd, J = 5.1, 2.3 Hz, 1H), 6.25 (dt, J = 23.2, 2.0 Hz, 1H), 4.82 - 4.61 (m, 1H), 4.49 - 4.29 (m, 2H), 4.20 (d, J = 3.9 Hz, 1H), 3.87 (d, J = 13.1 Hz, 3H), 3.60 (ddd, J = 90.2, 4.3, 2.4 Hz, 1H), 2.94 (ddd, J = 36.6, 6.4, 4.3 Hz, 1H), 2.81 (ddd, J = 28.6, 6.4, 2.4 Hz, 1H), 2.52 (d, J = 2.1 Hz, 3H).	470.20

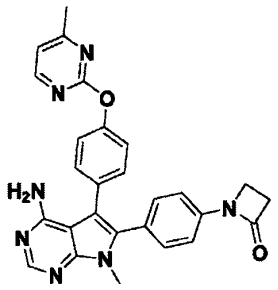
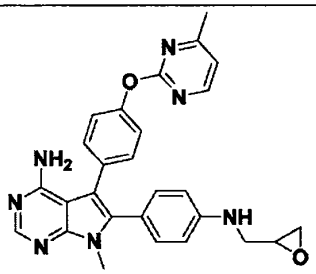
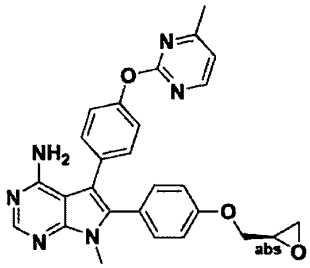
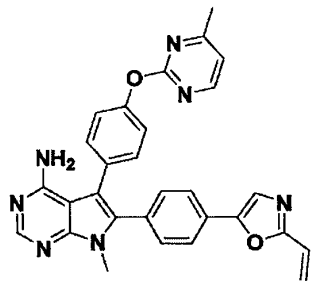
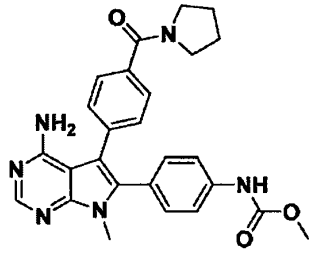
[1270]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-氰基乙酰胺		1H NMR (400 MHz, DMSO-d6) δ10.42 (s, 1H), 8.21 (s, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.33 - 7.22 (m, 4H), 6.00 (s, 2H), 3.92 (s, 2H), 3.61 (s, 3H), 3.44 (dt, J = 19.1, 6.5 Hz, 4H), 1.84 (dq, J = 18.4, 6.8 Hz, 4H).	480.20
N-(4-(4-氨基-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4,5-二氢呋喃-3-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.75 - 7.64 (m, 2H), 7.51 (d, J = 1.9 Hz, 1H), 7.29 (d, J = 8.4 Hz, 4H), 7.21 - 7.14 (m, 3H), 5.90 (s, 1H), 4.52 (t, J = 9.7 Hz, 2H), 3.61 (s, 3H), 3.06 - 2.75 (m, 2H), 2.41 (s, 3H).	520.25
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2,5-二氢呋喃-3-甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.75 - 7.68 (m, 2H), 7.37 - 7.25 (m, 4H), 7.22 - 7.12 (m, 3H), 6.97 - 6.92 (m, 1H), 5.93 (s, 2H), 4.77 (h, J = 2.9 Hz, 4H), 3.61 (s, 3H), 2.41 (s, 3H).	520.20
5-(4-(4-氨基-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)噻唑-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.24 - 7.19 (m, 2H), 7.16 (d, J = 5.0 Hz, 1H), 3.67 (s, 3H), 2.41 (s, 3H).	517.20
5-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)恶唑-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.23 - 7.13 (m, 3H), 5.98 (s, 1H), 3.67 (s, 3H), 2.41 (s, 3H).	501.15

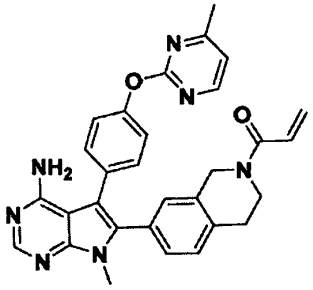
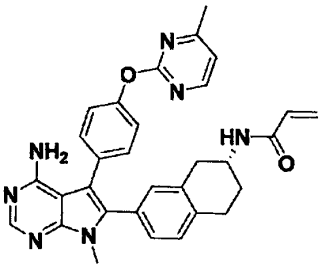
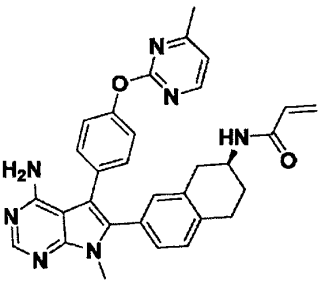
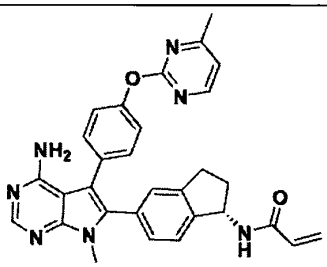
[1271]

化合物	结构	质子 NMR	MS [M+1]
7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(4-(2-乙烯基噻唑-5-基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.42 - 8.36 (m, 2H), 7.99 (s, 1H), 7.63 - 7.55 (m, 2H), 7.38 - 7.30 (m, 4H), 7.26 - 7.16 (m, 2H), 6.99 - 6.88 (m, 2H), 6.09 (d, *J* = 17.5 Hz, 1H), 5.61 (d, *J* = 10.9 Hz, 1H), 5.27 (s, 2H), 3.80 (s, 3H), 2.52 (s, 3H).	518.25
6-(4-(2-氯恶唑-5-基)苯基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.86 (s, 1H), 7.76 - 7.69 (m, 2H), 7.53 - 7.46 (m, 2H), 7.34 - 7.27 (m, 2H), 7.23 - 7.13 (m, 3H), 3.66 (s, 3H), 2.41 (s, 3H), 1.24 (s, 1H).	510.15
6-(4-(2-乙炔基恶唑-5-基)苯基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6)8.46 (s, 1H), 8.23 (s, 1H), 7.89 (s, 1H), 7.80-7.75 (m, 2H), 7.50 (s, 2H), 7.31 (m, 2H), 7.19 (s, 3H), 5.95 (s, 1H), 4.97 (s, 1H), 3.66 (s, 3H), 2.41 (s, 3H).	500.15
6-(2-氟嘧啶-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 1.5 Hz, 2H), 8.48 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.44 - 7.31 (m, 2H), 7.26 - 7.21 (m, 2H), 5.81 (s, 1H), 7.17 (d, J = 5.0 Hz, 1H), 3.70 (s, 3H), 2.42 (s, 3H).	429.10
(S)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(4-(环氧乙烷-2-基甲氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 5.0 Hz, 1H), 8.20 (s, 1H), 7.39 - 7.23 (m, 4H), 7.22 - 7.09 (m, 3H), 7.07 - 6.92 (m, 2H), 5.82 (d, *J* = 52.7 Hz, 2H), 4.36 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.86 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.58 (s, 3H), 3.17 (d, *J* = 5.3 Hz, 1H), 2.85 (t, *J* = 4.7 Hz, 1H), 2.76 - 2.61 (m, 1H), 2.42 (s, 3H).	481.20

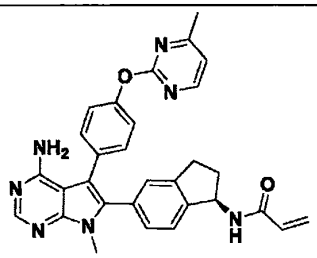
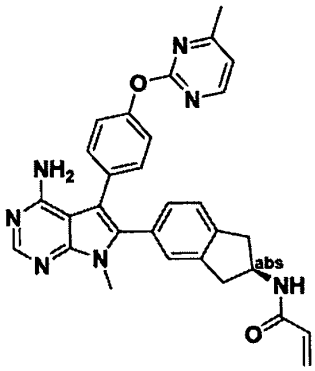
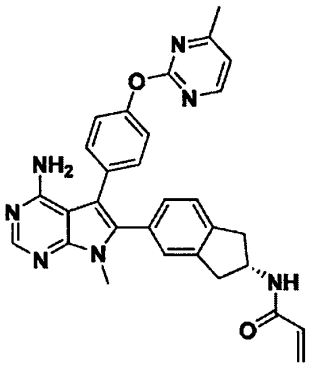
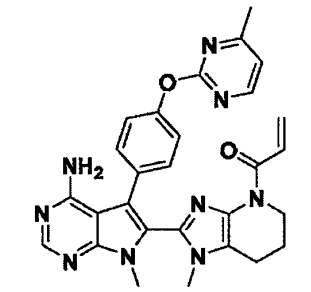
[1272]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)氮杂环丁-2-酮		1H NMR (400 MHz, DMSO-d6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.37 (s, 4H), 7.31 - 7.25 (m, 2H), 7.21 - 7.14 (m, 3H), 5.84 (d, J = 60.6 Hz, 1H), 3.65 (t, J = 4.5 Hz, 2H), 3.60 (s, 3H), 3.09 (t, J = 4.5 Hz, 2H), 2.41 (s, 3H).	478.15
7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(4-((环氧乙烷-2-基甲基)氨基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.47 (d, J = 5.0 Hz,1H), 8.17 (s, 1H), 7.33 - 7.24 (m, 2H), 7.21 - 7.12 (m, 3H), 7.11 - 7.00 (m, 2H), 6.64 (d, J = 8.5 Hz, 2H), 6.14 (t, J = 5.6 Hz, 1H), 5.81 (s, 1H), 3.58 (s, 3H), 3.40 - 3.33 (m, 1H), 3.09 (td, J = 7.6, 6.2, 3.5 Hz, 2H), 2.75 (dd, J = 5.1, 3.9 Hz, 1H), 2.60 (dd, J = 5.1, 2.3 Hz, 1H), 2.42 (s, 3H),	480.15
(R)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(4-(环氧乙烷-2-基甲氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.38 - 7.22 (m, 4H), 7.22 - 7.11 (m, 3H), 7.07 - 6.97 (m, 2H), 4.36 (dd, J = 11.4, 2.8 Hz, 1H), 3.86 (dd, J = 11.3, 6.6 Hz, 1H), 3.58 (s, 3H), 3.31 (s, 1H), 2.85 (dd, J = 5.1, 4.2 Hz, 1H), 2.72 (dd, J = 5.1, 2.7 Hz, 1H), 2.41 (s, 3H).	481.25
7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(4-(2-乙烯基恶唑-5-基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.84 - 7.76 (m, 3H), 7.51 - 7.45 (m, 2H), 7.35 - 7.27 (m, 2H), 7.23 - 7.12 (m, 3H), 6.70 (dd, J = 17.6, 11.2 Hz, 1H), 6.26 (dd, J = 17.6, 1.1 Hz, 1H), 6.03 (s, 1H), 5.91 (s, 1H), 5.79 - 5.72 (m, 1H), 3.66 (s, 3H), 2.40 (s, 3H).	502.15
(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)氨基甲酸甲酯		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.20 (s, 1H), 7.48 (dd, J = 8.7, 7.1 Hz, 4H), 7.32 - 7.18 (m, 4H), 3.67 (s, 3H), 3.60 (s, 3H), 3.43 (dt, J = 16.5, 6.5 Hz, 4H), 1.83 (dq, J = 18.3, 6.7 Hz, 4H).	471.25

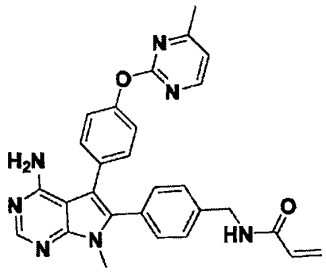
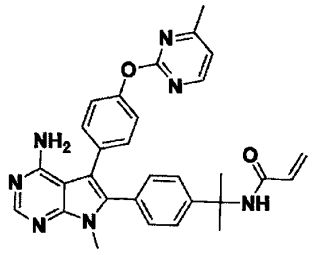
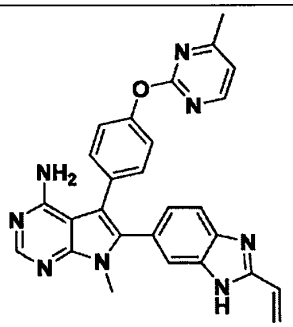
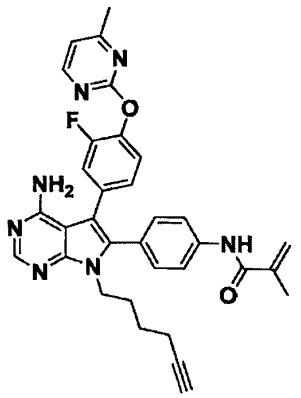
[1273]

化合物	结构	质子 NMR	MS [M+1]
1-(7-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,4-二氢异喹啉-2(1H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.36 - 7.26 (m, 2H), 7.25 - 7.09 (m, 6H), 6.89 (dd, J = 16.6, 10.6 Hz, 1H), 6.15 (dd, J = 16.7, 2.4 Hz, 1H), 5.72 (dd, J = 10.4, 2.4 Hz, 1H), 4.76 (d, J = 41.4 Hz, 2H), 3.78 (dt, J = 24.4, 5.9 Hz, 2H), 3.61 (s, 3H), 2.94 - 2.71 (m, 2H), 2.41 (s, 3H).	518.20
(R)-N-(7-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1,2,3,4-四氢萘-2-基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.23 - 8.14 (m, 2H), 7.38 - 7.29 (m, 2H), 7.24 - 7.07 (m, 6H), 6.26 (dd, J = 17.1, 10.0 Hz, 1H), 6.10 (dd, J = 17.1, 2.4 Hz, 1H), 5.97 - 5.69 (m, 1H), 5.59 (dd, J = 10.1, 2.4 Hz, 1H), 4.03 (s, 1H), 3.61 (s, 3H), 2.97 (dd, J = 16.6, 5.3 Hz, 1H), 2.85 (d, J = 11.2 Hz, 2H), 2.71 - 2.57 (m, 2H), 2.41 (s, 3H), 1.97 (d, J = 12.0 Hz, 1H), 1.76 - 1.62 (m, 1H).	532.25
(S)-N-(7-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1,2,3,4-四氢萘-2-基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.19 (d, J = 4.2 Hz, 2H), 7.35 - 7.27 (m, 2H), 7.26 - 7.08 (m, 6H), 6.33 - 6.23 (m, 1H), 6.12 (d, J = 2.3 Hz, 1H), 6.08 (d, J = 2.4 Hz, 1H), 5.59 (dd, J = 10.1, 2.4 Hz, 1H), 4.03 (s, 1H), 3.61 (s, 3H), 2.97 (dd, J = 16.5, 5.3 Hz, 1H), 2.85 (d, J = 11.2 Hz, 2H), 2.84 - 2.57 (m, 2H), 2.41 (s, 3H), 1.98 (d, J = 11.9 Hz, 1H), 1.67 (p, J = 9.8 Hz, 1H).	532.25
(S)-N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,3-二氢-1H-茚-1-基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 8.55 (d, J = 8.3 Hz, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.35 - 7.26 (m, 3H), 7.25 - 7.14 (m, 5H), 6.32 - 6.12 (m, 2H), 5.81 (s, 1H), 5.63 (dd, J = 9.9, 2.5 Hz, 1H), 5.39 (q, J = 8.0 Hz, 1H), 3.59 (s, 3H), 2.99 - 2.88 (m, 1H), 2.83 (dt, J = 16.2, 8.3 Hz, 1H), 2.45 (dt, J = 8.0, 3.8 Hz, 1H), 2.41 (s, 3H), 1.82 (dq, J = 12.5, 8.7 Hz, 1H).	518.25

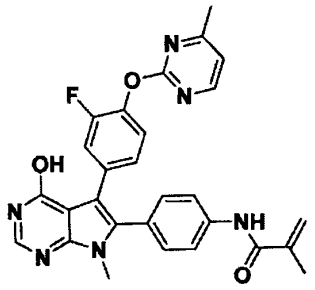
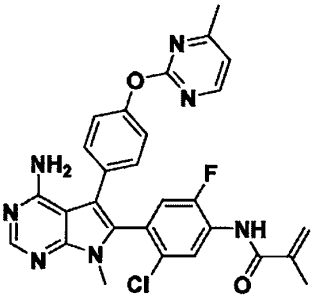
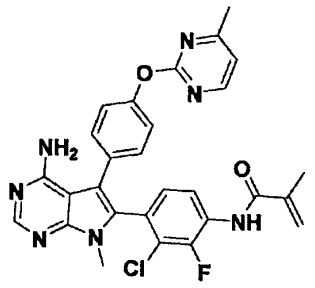
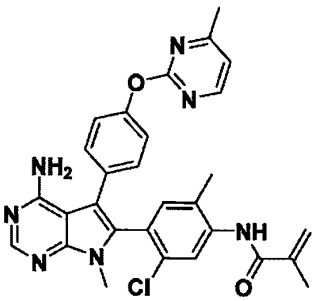
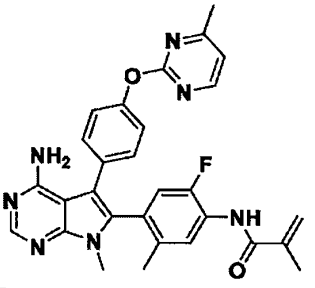
[1274]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,3-二氢-1H-茚-1-基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.30 - 7.15 (m, 5H), 7.13 - 7.06 (m, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.89 (dd, J = 16.7, 10.5 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.15 (dd, J = 16.7, 2.4 Hz, 1H), 5.88 (s, 2H), 5.72 (dd, J = 10.4, 2.4 Hz, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 3.80 (d, J = 6.3 Hz, 2H), 3.62 (s, 3H), 2.83 (s, 2H), 2.33 (s, 3H).	517.25
(R)-N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,3-二氢-1H-茚-2-基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 8.49 - 8.41 (m, 2H), 8.20 (s, 1H), 7.34 - 7.23 (m, 4H), 7.21 - 7.13 (m, 4H), 6.26 - 6.06 (m, 2H), 5.88 (s, 1H), 5.58 (dd, J = 9.9, 2.5 Hz, 1H), 4.56 (q, J = 6.6 Hz, 1H), 3.59 (s, 3H), 3.23 (ddd, J = 16.2, 12.9, 7.6 Hz, 2H), 2.81 (ddd, J = 16.8, 11.8, 5.6 Hz, 2H), 2.41 (s, 3H).	518.20
(S)-N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,3-二氢-1H-茚-2-基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 8.49 - 8.41 (m, 2H), 8.20 (s, 1H), 7.34 - 7.23 (m, 4H), 7.21 - 7.13 (m, 4H), 6.26 - 6.06 (m, 2H), 5.88 (s, 1H), 5.58 (dd, J = 9.9, 2.5 Hz, 1H), 4.56 (q, J = 6.6 Hz, 1H), 3.59 (s, 3H), 3.23 (ddd, J = 16.2, 12.9, 7.6 Hz, 2H), 2.81 (ddd, J = 16.8, 11.8, 5.6 Hz, 2H), 2.41 (s, 3H).	518.25
1-(2-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1,5,6,7-四氢-4H-咪唑并[4,5-b]吡啶-4-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.74 (dd, J = 28.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 5.2 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 5.77 - 5.69 (m, 1H), 3.83 (s, 2H), 3.66 (s, 3H), 2.99 (s, 3H), 2.58 (t, J = 6.4 Hz, 2H), 2.40 (s, 3H), 1.94 (s, 2H).	522.25

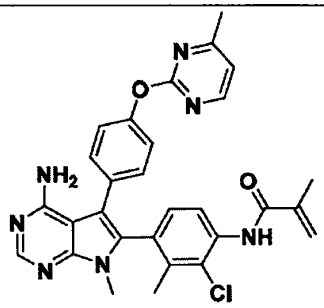
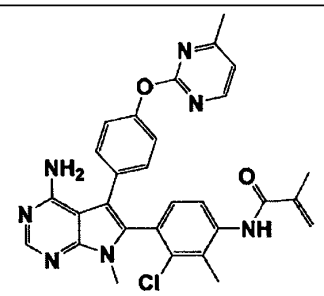
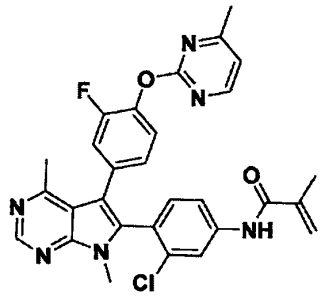
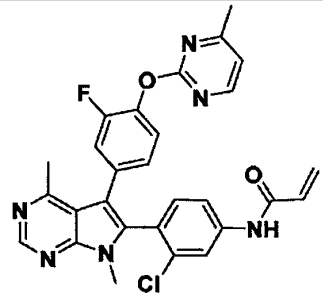
[1275]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯甲基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 8.65 (t, J = 6.1 Hz, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.33 - 7.27 (m, 4H), 7.21 - 7.13 (m, 3H), 6.30 (dd, J = 17.1, 10.1 Hz, 1H), 6.14 (dd, J = 17.1, 2.2 Hz, 1H), 5.89 (s, 1H), 5.64 (dd, J = 10.1, 2.3 Hz, 1H), 4.40 (d, J = 6.0 Hz, 2H), 3.59 (s, 3H), 2.41 (s, 3H).	492.20
N-(2-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙-2-基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.20 (s, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.23 (d, J = 2.0 Hz, 1H), 7.17 (dd, J = 8.3, 2.1 Hz, 1H), 7.15 - 7.07 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.57 (dd, J = 17.0, 10.2 Hz, 1H), 6.26 (dd, J = 17.0, 2.1 Hz, 1H), 6.14 - 5.86 (m, 1H), 5.77 (dd, J = 10.2, 2.0 Hz, 1H), 3.63 (s, 3H), 2.34 (s, 3H), 2.20 (s, 3H).	491.35
7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(2-乙烯基-1H-苯并[d]咪唑-6-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (d, J = 14.7 Hz, 1H), 8.44 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.62 (s, 1H), 7.55 - 7.34 (m, 1H), 7.34 - 7.24 (m, 2H), 7.21 - 7.04 (m, 4H), 6.77 (dd, J = 17.8, 11.2 Hz, 1H), 6.28 (d, J = 17.8 Hz, 1H), 5.88 (s, 1H), 5.69 (d, J = 11.4 Hz, 1H), 3.61 (s, 3H), 2.39 (s, 3H).	475.20
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-(己-5-炔-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.37 - 7.28 (m, 3H), 7.24 - 7.15 (m, 2H), 7.11 (d, J = 8.1 Hz, 1H), 6.01 (s, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 4.11 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 2.7 Hz, 1H), 2.42 (s, 3H), 2.04 (td, J = 7.0, 2.6 Hz, 2H), 1.96 (t, J = 1.2 Hz, 3H), 1.60 (q, J = 7.4 Hz, 2H), 1.26 (q, J = 7.3 Hz, 2H).	576.25

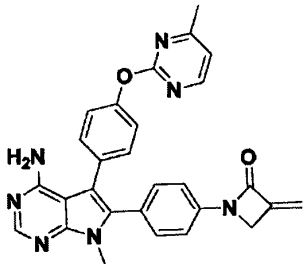
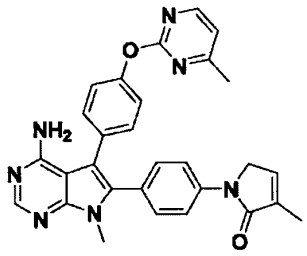
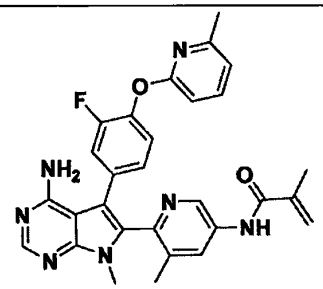
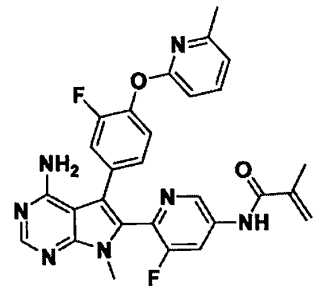
[1276]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4-羟基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (d, J = 3.8 Hz, 1H), 9.95 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.00 (d, J = 3.7 Hz, 1H), 7.82 - 7.70 (m, 2H), 7.38 - 7.23 (m, 3H), 7.20 - 7.11 (m, 2H), 7.06 - 6.99 (m, 1H), 5.81 (d, J = 1.4 Hz, 1H), 5.54 (t, J = 1.5 Hz, 1H), 3.57 (s, 3H), 2.42 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	511.20
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-5-氯-2-氟苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) 9.78 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.93 (d, J = 7.0 Hz, 1H), 7.52 (d, J = 10.5 Hz, 1H), 7.32-7.25 (m, 2H), 7.23 -7.12 (m, 3H), 6.38-5.88(s,1H),5.88 (s, 1H), 5.60 (s, 1H), 3.51 (s, 3H), 2.40 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H).	544.15
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氯-2-氟苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.42 (s, 4H), 7.30 (d, J = 8.5 Hz, 2H), 7.22 - 7.12 (m, 3H), 5.82 (d, J = 1.6 Hz, 1H), 4.27 (s, 2H), 3.61 (s, 3H), 2.41 (s, 3H).	544.30
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-5-氯-2-甲基苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) 9.38 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.68 (s, 1H), 7.34 (s, 1H), 7.32-7.25 (m, 2H), 7.22-7.11 (m, 3H), 5.95 (s, 2H), 5.55 (t, J = 1.5 Hz, 1H), 3.48 (s, 3H), 2.40 (s, 3H), 2.18 (s, 3H), 1.97 (t, J = 1.3 Hz, 3H).	540.15
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氟-5-甲基苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6)9.88 (s, 1H), 8.57-8.39 (m, 2H), 7.85-7.59 (m, 1H), 7.35 (dd, J = 8.4, 1.5 Hz, 1H), 7.31-7.25 (m, 2H), 7.24-7.19 (m, 2H), 7.16 (d, J = 5.0 Hz, 1H), 5.90 (s, 1H), 5.62 (d, J = 1.8 Hz, 1H), 3.58 (s, 3H), 2.41 (s, 3H), 1.96 (d, J = 1.2 Hz, 3H).	524.35

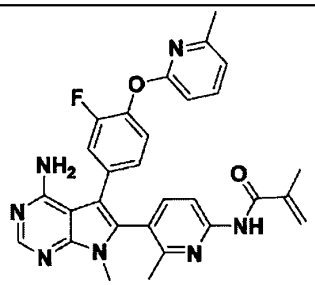
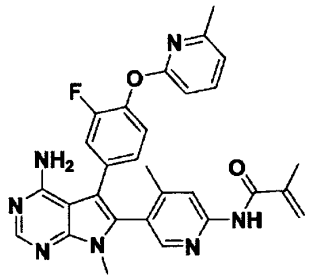
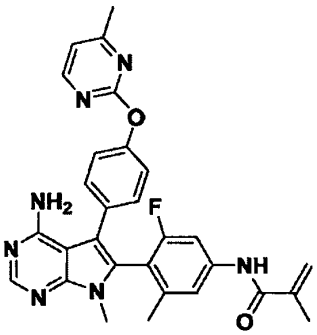
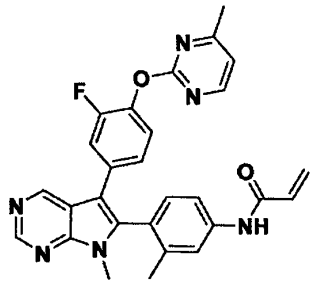
[1277]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.29 - 7.22 (m, 2H), 7.19 - 7.11 (m, 3H), 5.92 (s, 2H), 5.56 (t, J = 1.5 Hz, 1H), 3.45 (s, 3H), 2.40 (s, 3H), 2.06 (s, 3H), 1.97 (t, J = 1.2 Hz, 3H).	540.20
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氯-2-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.44 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.38 - 7.24 (m, 4H), 7.20 - 7.11 (m, 3H), 5.88 (s, 1H), 5.55 (t, J = 1.5 Hz, 1H), 3.46 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	540.20
N-(3-氯-4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.13 (s, 1H), 8.77 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.5, 2.1 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 6.0 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 5.84 (s, 1H), 5.59 (s, 1H), 3.58 (s, 3H), 2.41 (d, J = 8.0 Hz, 6H), 1.96 (d, J = 1.3 Hz, 3H).	543.20
N-(3-氯-4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.51 (s, 1H), 8.77 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H), 7.61 (dd, J = 8.5, 2.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.38 - 7.25 (m, 2H), 7.16 (dd, J = 16.1, 6.7 Hz, 2H), 6.43 (dd, J = 16.9, 10.0 Hz, 1H), 6.31 (dd, J = 17.0, 2.1 Hz, 1H), 5.84 (dd, J = 9.9, 2.1 Hz, 1H), 3.58 (s, 3H), 2.41 (d, J = 8.9 Hz, 6H).	529.20

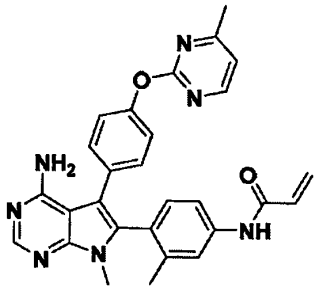
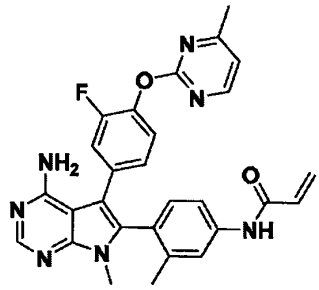
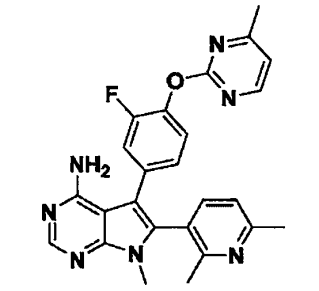
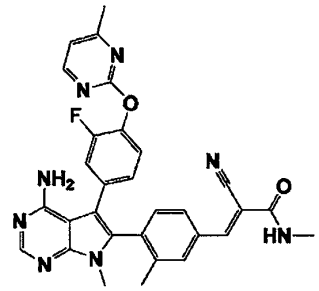
[1278]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基氮杂环丁-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 11.7 Hz, 1H), 8.13 (s, 1H), 7.63 (d, J = 2.7 Hz, 1H), 6.59 (s, 2H), 5.69 (d, J = 30.0 Hz, 2H), 4.42 (d, J = 1.1 Hz, 1H), 3.51 - 3.38 (m, 2H), 3.37 (d, J = 1.4 Hz, 3H), 3.28 (s, 0H), 2.75 (s, 0H), 2.68 (p, J = 1.8 Hz, 1H), 2.34 (p, J = 1.9 Hz, 1H), 2.20 (d, J = 7.1 Hz, 2H), 1.93 (d, J = 9.1 Hz, 2H), 1.85 (q, J = 6.1 Hz, 1H), 1.82 - 1.69 (m, 2H), 1.60 (d, J = 7.0 Hz, 2H).	490.15
1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-甲基-1,5-二氢-2H-吡咯-2-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.41 (d, J = 5.1 Hz, 1H), 8.22 (s, 1H), 7.90 - 7.80 (m, 2H), 7.42 - 7.34 (m, 4H), 7.22 - 7.12 (m, 3H), 7.03 (q, J = 1.8 Hz, 1H), 4.45 (p, J = 2.0 Hz, 2H), 3.72 (s, 3H), 2.50 (s, 3H), 1.94 (q, J = 1.9 Hz, 3H).	504.20
N-(6-(4-氨基-5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-5-甲基吡啶-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.24 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.78 - 7.71 (m, 1H), 7.24 (t, J = 8.4 Hz, 1H), 7.07 - 6.95 (m, 3H), 6.86 (d, J = 8.2 Hz, 1H), 6.21 (s, 1H), 5.87 (s, 1H), 5.60 (s, 1H), 3.51 (s, 3H), 2.30 (s, 3H), 1.97 (t, J = 1.2 Hz, 3H), 1.83 (s, 3H).	524.35
N-(6-(4-氨基-5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-5-氟吡啶-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.89 - 8.84 (m, 1H), 8.25 (s, 1H), 8.13 (dd, J = 11.9, 2.0 Hz, 1H), 7.75 (dd, J = 8.2, 7.3 Hz, 1H), 7.27 (t, J = 8.4 Hz, 1H), 7.14 (dd, J = 11.5, 2.1 Hz, 1H), 7.07 - 6.98 (m, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.22 (s, 1H), 5.90 (s, 1H), 5.68 - 5.63 (m, 1H), 3.65 (s, 3H), 2.31 (s, 3H), 1.97 (t, J = 1.2 Hz, 3H).	528.35

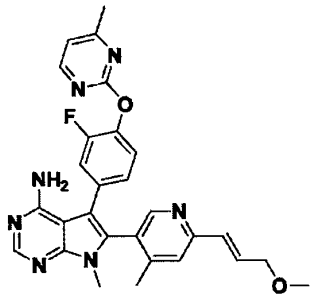
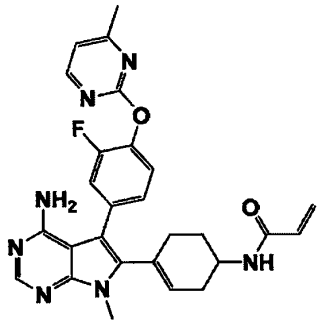
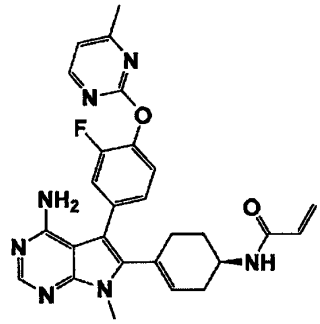
[1279]

化合物	结构	质子 NMR	MS [M+1]
N-(5-(4-氨基-5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-6-甲基吡啶-2-基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.32 (d, J = 13.1 Hz, 1H), 8.23 (s, 1H), 8.11 - 8.00 (m, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.2, 7.4 Hz, 1H), 7.25 (t, J = 8.4 Hz, 1H), 7.13 (dd, J = 11.6, 2.0 Hz, 1H), 7.07 - 6.97 (m, 2H), 6.84 (d, J = 8.2 Hz, 1H), 6.13 (s, 1H), 5.94 (s, 1H), 5.58 - 5.53 (m, 1H), 3.50 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	524.21
N-(5-(4-氨基-5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-4-甲基吡啶-2-基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 8.23 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.77 - 7.69 (m, 1H), 7.25 (t, J = 8.4 Hz, 1H), 7.13 (dd, J = 11.5, 2.1 Hz, 1H), 7.05 - 6.97 (m, 2H), 6.85 (d, J = 8.2 Hz, 1H), 5.94 (s, 1H), 5.58 - 5.53 (m, 1H), 3.50 (s, 3H), 2.28 (s, 3H), 2.09 (s, 3H), 1.96 (t, J = 1.2 Hz, 3H).	524.21
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟-5-甲基苯基)甲基丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.66 (dd, J = 11.6, 2.0 Hz, 1H), 7.44 - 7.42 (m, 1H), 7.26 - 7.22 (m, 2H), 7.21 - 7.13 (m, 3H), 6.01 (s, 1H), 5.82 (s, 1H), 5.57 (s, 1H), 3.45 (s, 3H), 2.40 (s, 3H), 1.96 - 1.89 (m, 6H).	524.25
N-(4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.23 (s, 1H), 8.94 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 7.76 -7.67 (m, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.26 -7.15 (m, 3H), 6.47 (dd, J = 17.0, 10.1 Hz, 1H), 6.30 (dd, J = 17.0, 2.1 Hz, 1H), 5.80 (dd, J = 10.1, 2.1 Hz, 1H), 3.55 (s, 3H), 2.42 (s, 3H), 2.00 (s, 3H).	495.20

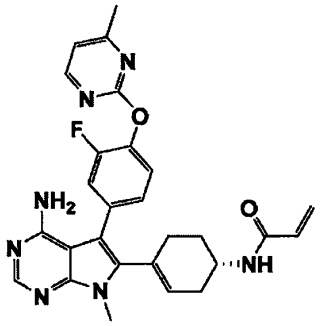
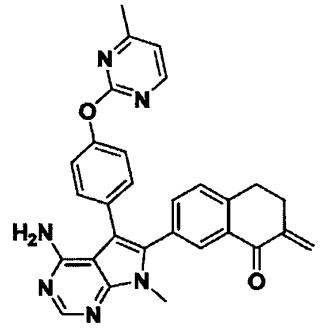
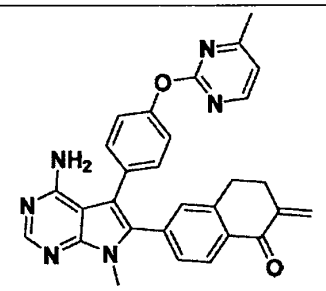
[1280]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) 10.22 (s, 1H), 8.45 (d, J = 4.3 Hz, 1H), 8.21 (d, J = 3.0 Hz, 1H), 7.60 (d, J = 13.2 Hz, 2H), 7.35 -7.28 (m, 1H), 7.28 -7.22 (m, 2H), 7.15 (d, J = 7.4 Hz, 3H), 6.45 (dd, J = 17.9, 9.9 Hz, 1H), 6.27 (d, J = 16.8 Hz, 1H), 5.78 (d, J = 10.2 Hz, 1H),5.56 (s, 1H), 3.39 (s, 3H), 2.40 (d, J = 3.0 Hz, 3H), 1.97 (d, J = 3.0 Hz, 3H).	492.20
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6)10.24 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.66 -7.57 (m, 2H), 7.32 (t, J = 8.4 Hz, 2H), 7.17 (d, J = 5.0 Hz, 1H), 7.12 (dd, J = 11.6, 2.1 Hz, 1H), 7.06 (dd, J = 8.4, 2.0 Hz, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 6.08 -6.01 (m, 1H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.43 (s, 3H), 2.41 (s, 3H), 1.96 (s, 3H).	510.10
6-(2,6-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ8.47 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.24-7.11 (m, 3H), 7.08-7.01 (m, 1H), 3.44 (s, 3H), 2.48 (s, 3H), 2.41 (s, 3H), 2.12 (s, 3H).	456.20
(2E)-3-[4-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基]-2-氰基-N-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.41 (d, J = 4.6 Hz, 1H), 8.24 (s, 1H), 8.17 (s, 1H), 7.94 - 7.89 (m, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.62 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.21 - 7.11 (m, 2H), 7.06 (ddd, J = 8.3, 2.1, 0.8 Hz, 1H), 6.09 (s, 1H), 3.46 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 2.40 (s, 3H), 2.04 (s, 3H).	549.35

[1281]

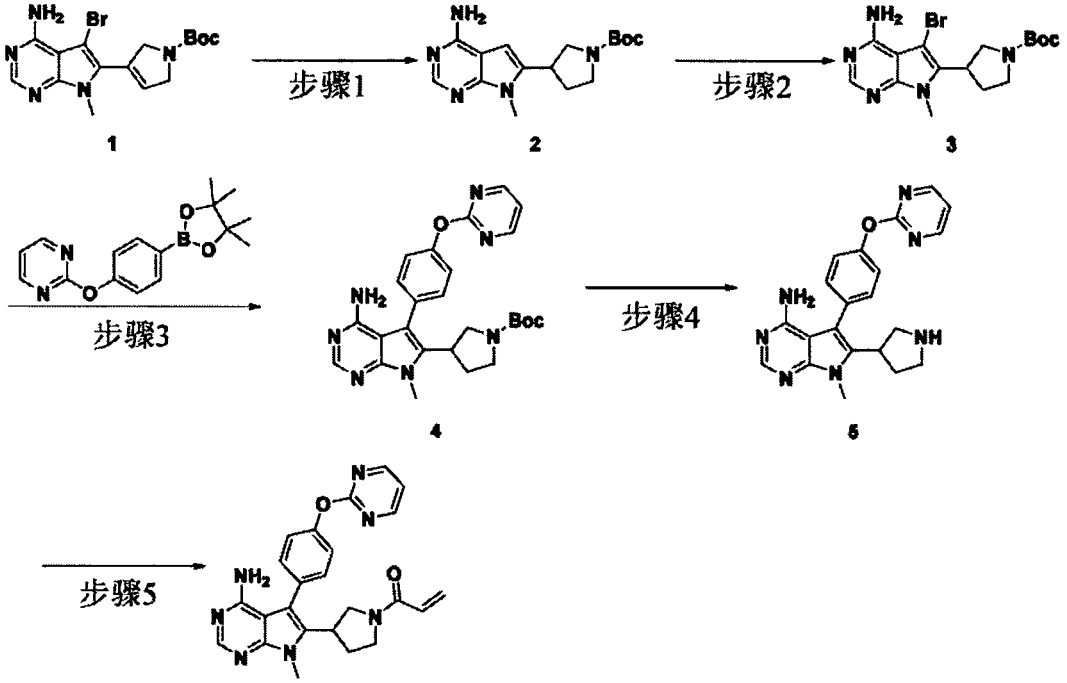
化合物	结构	质子 NMR	MS [M+1]
(E)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(6-(3-甲氧基丙-1-烯-1-基)-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01 (s, 3H), 2.40 (s, 3H), 3.46 (s, 3H), 4.11 (d, J = 5.1 Hz, 2H), 6.68 (s, 1H), 6.79 - 6.88 (m, 1H), 7.05 (d, J = 8.3 Hz, 1H), 7.12 - 7.21 (m, 2H), 7.32 (t, J = 8.4 Hz, 1H), 7.43 (s, 1H), 8.23 (s, 1H), 8.46 (d, J = 4.9 Hz, 2H).	512.4
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)环己-3-烯-1-基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 5.0 Hz, 1H), 8.17 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.32 (dd, J = 11.5, 2.1 Hz, 1H), 7.26 - 7.17 (m, 2H), 6.22 (dd, J = 17.0, 10.0 Hz, 1H), 6.07 (dd, J = 17.1, 2.3 Hz, 2H), 5.84 (d, J = 4.4 Hz, 1H), 5.57 (dd, J = 10.0, 2.4 Hz, 1H), 3.91 (s, 1H), 3.66 (s, 3H), 2.42 (m, 4H), 2.21 (s, 1H), 2.08 (d, J = 15.5 Hz, 2H), 1.78 (d, J = 25.3 Hz, 1H), 1.53 (dd, J = 11.5, 5.2 Hz, 1H).	500.10
(R)-N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)环己-3-烯-1-基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 5.0 Hz, 1H), 8.16 (s, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.32 (dd, J = 11.4, 2.1 Hz, 1H), 7.26 - 7.17 (m, 2H), 6.22 (dd, J = 17.1, 10.1 Hz, 1H), 6.07 (dd, J = 17.1, 2.4 Hz, 1H), 6.00 (s, 1H), 5.83 (d, J = 4.6 Hz, 1H), 5.56 (dd, J = 10.1, 2.3 Hz, 1H), 3.91 (s, 1H), 3.65 (s, 3H), 2.42 (s, 3H), 2.27 (d, J = 45.4 Hz, 1H), 2.08 (d, J = 15.3 Hz, 2H), 1.89 - 1.73 (m, 1H), 1.54 (dd, J = 11.3, 5.2 Hz, 1H).	500.25

[1282]

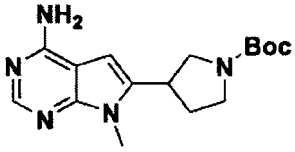
化合物	结构	质子 NMR	MS [M+1]
(S)-N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)环己-3-烯-1-基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 5.0 Hz, 1H), 8.16 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 8.3 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.21 (dd, J = 13.1, 6.7 Hz, 2H), 6.22 (dd, J = 17.1, 10.1 Hz, 1H), 6.07 (dd, J = 17.1, 2.3 Hz, 1H), 5.98 (s, 1H), 5.84 (s, 1H), 5.56 (dd, J = 10.0, 2.4 Hz, 1H), 3.91 (s, 1H), 3.65 (s, 3H), 2.42 (s, 4H), 2.21 (s, 1H), 2.15 - 1.97 (m, 2H), 1.83 (d, J = 11.9 Hz, 1H), 1.54 (dd, J = 11.5, 5.2 Hz, 1H).	500.25
7-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-亚甲基-3,4-二氢萘-1(2H)-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.60 (dd, J = 7.9, 2.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.22 - 7.10 (m, 3H), 6.05 (d, J = 2.1 Hz, 1H), 5.93 (s, 2H), 5.56 (d, J = 1.9 Hz, 1H), 3.61 (s, 3H), 3.02 (t, J = 6.4 Hz, 2H), 2.90 - 2.82 (m, 2H), 2.40 (s, 3H).	489.30
6-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-亚甲基-3,4-二氢萘-1(2H)-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.36 (dd, J = 8.0, 1.7 Hz, 1H), 7.35 -7.27 (m, 2H), 7.24- 7.13 (m, 3H), 6.06 (d, J = 2.1 Hz, 1H), 5.99 (s, 2H), 5.56 (d, J = 2.0 Hz, 1H), 3.68 (s, 3H), 2.96 (t, J = 6.3 Hz, 2H), 2.84 (t, J = 6.1 Hz, 2H), 2.41 (s, 3H).	489.35

[1283] 实例14

[1284] 流程12

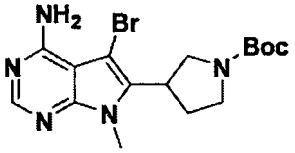
[1285] 

[1286] 3-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲酸叔丁酯

[1287] 

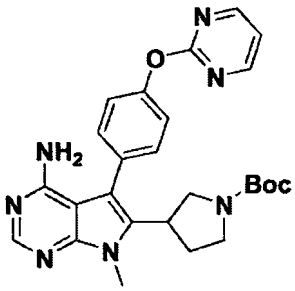
[1288] 步骤1:向可再密封的反应瓶中装入3-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(1.2g,3.07mmol)、Pd-C(120mg,1.2mol)及搅拌棒,随后抽真空且用氢气吹扫三次。添加MeOH(20mL),且在50℃下搅拌混合物整夜。反应混合物经由Celite®垫过滤,所述垫用水洗涤,且真空浓缩滤液,产生呈灰白色固体状的3-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-甲酸叔丁酯(0.9g,91.8%)。

[1289] 3-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲酸叔丁酯

[1290] 

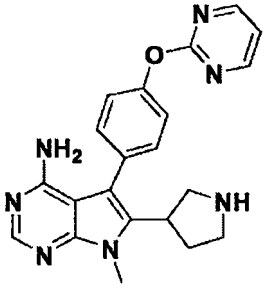
[1291] 步骤2:向圆底烧瓶中装入3-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-甲酸叔丁酯(300mg,945μmol)、NBS(168mg,945μmol)及搅拌棒。添加二氯甲烷(5mL),且在室温下搅拌溶液30分钟。反应混合物用水(10mL)稀释,且水相用二氯甲烷(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩,产生呈浅黄色固体状的3-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-吡咯烷-1-甲酸叔丁酯(230mg,61.4%)。

[1292] 3-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲酸叔丁酯

[1293] 

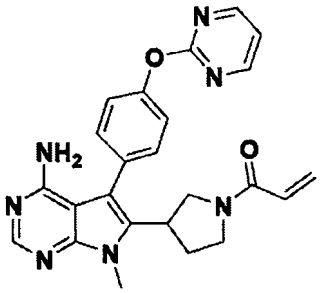
[1294] 步骤3:向可再密封的反应瓶中装入3-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-甲酸叔丁酯(200mg,504μmol)、2-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]嘧啶(165mg,554μmol)、Pd(dtbpf)Cl2(32.8mg,50.4μmol)、K3PO4(320mg,1.51mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF/水(2mL),且在90℃下搅拌混合物2小时。反应混合物用水(10mL)稀释,且水相用二氯甲烷(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(5g柱;用二氯甲烷/甲醇/0.1%三乙胺洗脱;比率)。真空浓缩,产生呈淡棕色固体状的3-{4-氨基-7-甲基-5-[4-(嘧啶-2-基氧基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-甲酸叔丁酯(100mg,40.7%)。

[1295] 7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-6-(吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1296] 

[1297] 步骤4:向圆底烧瓶中装入3-{4-氨基-7-甲基-5-[4-(嘧啶-2-基氧基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-甲酸叔丁酯(200mg,410μmol)及搅拌棒。添加TFA/DCM(1/4mL),且在室温下搅拌溶液30分钟。真空浓缩反应混合物。然后溶解于饱和NaHCO3中,用DCM萃取三次。合并的有机层经无水Na_2SO_4脱水。过滤且蒸发,得到呈灰白色固体状的7-甲基-5-[4-(嘧啶-2-基氧基)苯基]-6-(吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(150mg,94.4%)。

[1298] 1-(3-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮

[1299] 

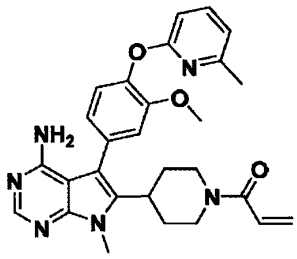
[1300] 步骤5:向圆底烧瓶中装入7-甲基-5-[4-(嘧啶-2-基氧基)苯基]-6-(吡咯烷-3-

基)-7H-吡咯并[2,3-d]嘧啶-4-胺(50mg,129μmol)、TEA(39.0mg,387μmol)、二氯甲烷(4mL)及搅拌棒。在-30℃下添加丙-2-烯酰氯(10.4mg,116μmol),且在-30℃下搅拌溶液30分钟。反应混合物经由Celite®垫过滤,所述垫用DCM洗涤且真空浓缩滤液。所得粗物质通过HPLC纯化(乙腈/水/0.1%甲酸)。冻干产生呈白色无定形固体状的1-(3-{4-氨基-7-甲基-5-[4-(嘧啶-2-基氧基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮(5.92mg,11.6%)。

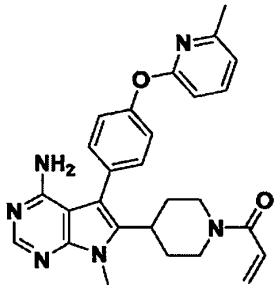
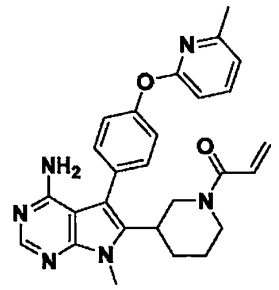
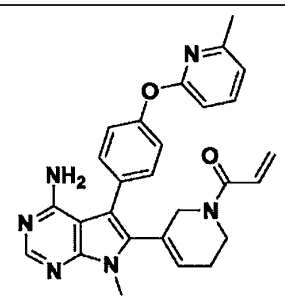
[1301] 根据实例14的方法制备的其它化合物描绘于下表13中。

[1302] 表13.其它示例性化合物

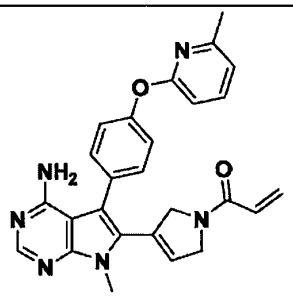
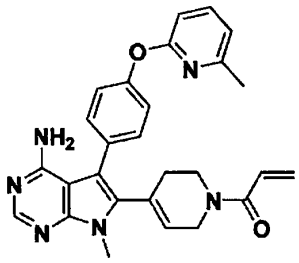
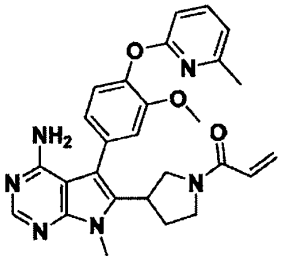
[1303]

化合物	结构	质子 NMR	MS [M+1]
1-[4-(4-氨基-5-{3-甲氧基-4-[(6-甲基吡啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基]丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.10 - 7.05 (m, 1H), 6.94 (d, J = 7.3 Hz, 2H), 6.76 (dd, J = 16.7, 10.5 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.04 (dd, J = 16.7, 2.4 Hz, 1H), 5.61 (dd, J = 10.4, 2.5 Hz, 2H), 4.47 (s, 1H), 4.13 - 4.06 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.09 (s, 2H), 2.64 (s, 2H), 2.31 (s, 3H), 1.83 (s, 2H), 1.57 (s, 2H).	498.587

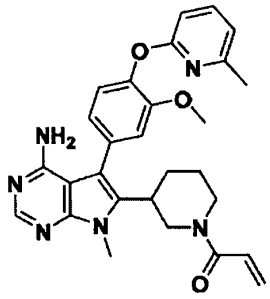
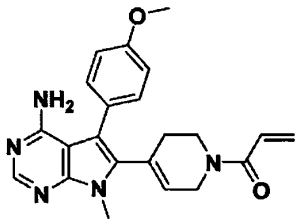
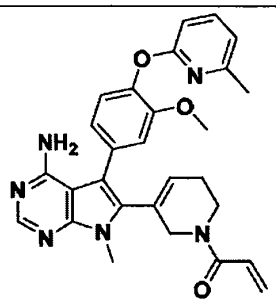
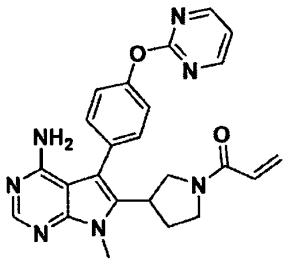
[1304]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.58 (dd, *J* = 16.8, 10.6 Hz, 1H), 6.28 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.70 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.87 - 4.83 (m, 2H), 4.79 (s, 1H), 4.08 (d, *J* = 13.6 Hz, 1H), 3.88 (s, 3H), 3.18 - 3.03 (m, 2H), 2.64 (s, 1H), 2.50 (s, 3H), 1.83 (s, 2H), 1.75 (s, 2H).	469.25
1-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基]丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 9.1 Hz, 1H), 6.84 - 6.75 (m, 1H), 6.08 (t, *J* = 17.7 Hz, 1H), 5.67 (t, *J* = 9.9 Hz, 1H), 4.51-4.45 (d, *J* = 12.5 Hz, 1H), 4.15 - 4.07 (d, *J* = 13.4 Hz, 1H), 3.84 (s, 3H), 3.17 - 3.07 (m, 1H), 2.97 (s, 1H), 2.87 - 2.61 (t, *J* = 12.2 Hz, 1H), 2.42 - 2.35 (s, 3H), 1.90 (d, *J* = 12.6 Hz, 1H), 1.67 (s, 2H), 1.41 (d, *J* = 13.9 Hz, 2H), 1.18 (t, *J* = 7.3 Hz, 1H).	469.35
1-[5-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-1,2,3,6-四氢吡啶-1-基]丙-2-烯-1-酮		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.34 (s, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.67 - 6.56 (m, 1H), 6.33 - 6.20 (d, *J* = 16.6 Hz, 1H), 6.03 (s, 1H), 5.75 (d, *J* = 10.6 Hz, 1H), 5.61 (d, *J* = 10.4 Hz, 1H), 5.44 (s, 1H) , 4.14 (s, 1H), 3.91 (s, 1H), 3.79 (s, 3H), 3.77 (s, 1H), 3.64 (s, 1H), 2.48 (s, 3H), 2.43 (s, 1H), 2.39 (s, 1H).	467.35

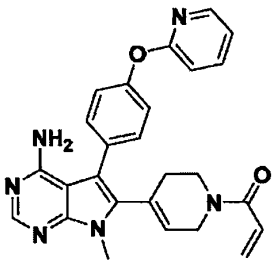
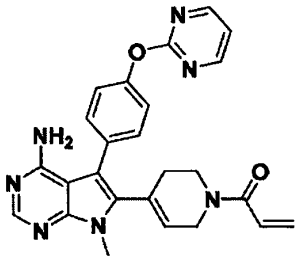
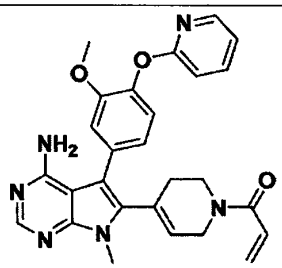
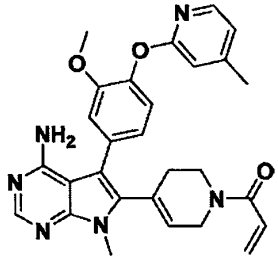
[1305]

化合物	结构	质子 NMR	MS [M+1]
1-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基]丙-2-烯-1-酮		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.36 (d, *J* = 3.2 Hz, 1H), 7.70 - 7.59 (m, 1H), 7.40 (dd, *J* = 11.3, 8.3 Hz, 2H), 7.23 (dd, *J* = 11.3, 8.2 Hz, 2H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.79 - 6.70 (m, 1H), 6.47-6.37 (m, 1H), 6.24 - 6.11 (m, 1H), 5.96 (s, 1H), 5.79 - 5.64 (m, 1H), 5.02 (s, 2H), 4.52 (s, 2H), 4.32 (s, 1H), 4.22 (s, 1H), 3.88 (d, *J* = 10.2 Hz, 3H), 2.49 (d, *J* = 9.9 Hz, 3H).	453.30
1-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.16 (s, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.88 - 6.70 (m, 2H), 6.12 (d, J = 16.7 Hz, 1H), 5.97 (s, 1H), 5.92 (s, 1H), 5.69 (t, J = 9.4 Hz, 1H), 4.23 (s, 1H), 4.14 (s, 1H), 3.66 (m, 5H), 2.36 (s, 3H), 2.13 (s, 2H).	467.2
1-(3-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, *J* = 1.6 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.26 - 7.07 (m, 2H), 6.96 (dd, *J* = 15.4, 7.5 Hz, 3H), 6.70 (dd, *J* = 8.2, 5.8 Hz, 1H), 6.58 - 6.39 (m, 1H), 6.10 (dd, *J* = 16.9, 2.6 Hz, 1H), 5.69 - 5.57 (m, 1H), 3.97 (t, *J* = 9.2 Hz, 1H), 3.79 (d, *J* = 6.4 Hz, 4H), 3.73 - 3.63 (m, 4H), 3.55 (dq, *J* = 17.8, 9.8, 9.2 Hz, 2H), 2.30 (d, *J* = 5.6 Hz, 3H), 2.21 - 1.89 (m, 2H).	485.15

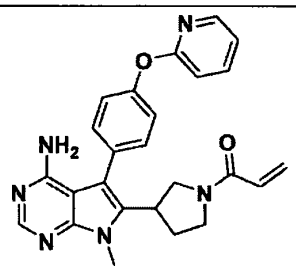
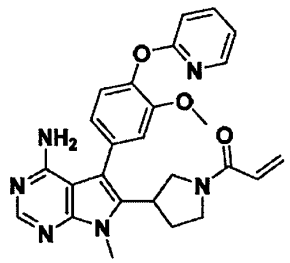
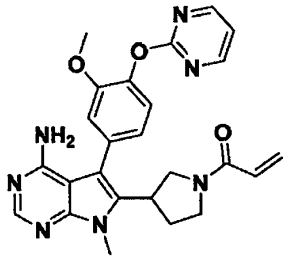
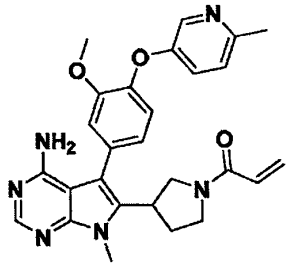
[1306]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.13 (s, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.88 - 6.71 (m, 2H), 6.09 (t, J = 17.2 Hz, 1H), 5.68 (d, J = 10.9 Hz, 1H), 4.57 - 4.47 (d, 1H), 4.19 - 4.09 (d, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.17 - 2.98 (d, 2H), 2.72 - 2.43 (d, 1H), 2.28 (s, 3H), 1.94 (d, J = 12.6 Hz, 1H), 1.71 (s, 2H), 1.41 (s, 1H).	499.2
1-(4-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.21 (s, 1H), 7.33 - 7.25 (m, 2H), 7.06 - 6.99 (m, 2H), 6.79 (ddd, J = 21.6, 16.7, 10.4 Hz, 1H), 6.13 (dt, J = 16.7, 3.6 Hz, 1H), 5.92 (d, 1H), 5.75 - 5.64 (m, 1H), 4.22 (s, 1H), 4.13 (s, 1H), 3.80 (s, 3H), 3.66 (m, 5H), 2.08 (s, 2H).	390.2
1-(5-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.18 (s, 1H), 7.66 (dt, J = 11.8, 7.8 Hz, 1H), 7.17 (m, 1H), 7.11 (d, J = 1.9 Hz, 1H), 7.02 - 6.91 (m, 2H), 6.85 (dd, J = 16.6, 10.4 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.31 (dd, J = 16.6, 10.4 Hz, 1H), 6.20 -5.95 (m, J = 16.1 Hz, 3H), 5.75 -5.52 (d, J = 10.5 Hz, 1H), 4.01 (s, 2H), 3.71 - 3.62 (m, 8H), 2.30 (d, J = 2.6 Hz, 5H).	497.3
1-(3-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (t, J = 4.5 Hz, 2H), 8.13 (d, J = 1.8 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.36 - 7.28 (m, 3H), 6.51 (ddd, J = 34.2, 16.8, 10.4 Hz, 1H), 6.11 (ddd, J = 16.8, 5.6, 2.4 Hz, 1H), 5.70 - 5.59 (m, 1H), 3.95 (t, J = 9.2 Hz, 1H), 3.80 (d, J = 6.8 Hz, 3H), 3.77 - 3.45 (m, 1H), 2.27 - 1.97 (m, 2H).	442.25

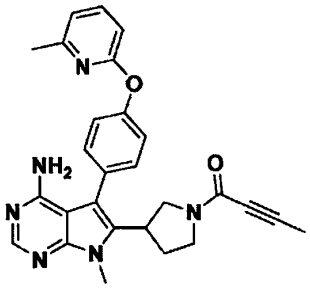
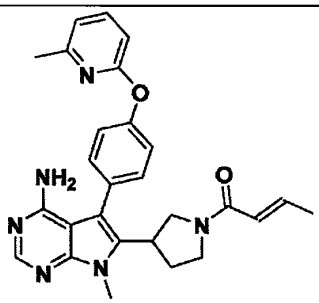
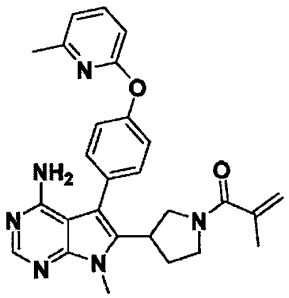
[1307]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-7-甲基-5-(4-(吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.23 - 8.10 (m, 2H), 7.92 - 7.82 (m, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.25 - 7.10 (m, 3H), 7.06 (d, J = 8.3 Hz, 1H), 6.78 (ddd, J = 25.5, 16.6, 10.4 Hz, 1H), 6.12 (dt, J = 16.4, 3.7 Hz, 1H), 5.94 (d, J = 24.1 Hz, 2H), 5.69 (t, J = 9.0 Hz, 1H), 4.26 - 4.08 (m, 2H), 3.63 (d, J = 12.5 Hz, 4H), 2.13 (s, 2H).	453.1
1-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J = 4.7 Hz, 2H), 8.17 (s, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.30 (q, J = 4.0, 3.2 Hz, 3H), 6.80 (ddd, J = 26.5, 16.7, 10.5 Hz, 1H), 6.12 (d, J = 16.8 Hz, 1H), 5.99 (s, 1H), 5.93 (s, 1H), 5.69 (t, J = 9.7 Hz, 1H), 4.23 (s, 1H), 4.14 (s, 1H), 3.66 (s, 3H), 3.62 (s, 0H), 3.07 (s, 1H), 2.15 (s, 2H), 1.17 (t, J = 7.3 Hz, 1H).	454.3
1-(4-(4-氨基-5-(3-甲氧基-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.20 - 8.06 (m, 2H), 7.88 - 7.75 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.09 (dd, J = 7.0, 4.8 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 6.80 (ddd, J = 27.3, 16.6, 10.3 Hz, 1H), 6.05 (dd, J = 56.4, 20.5 Hz, 3H), 5.68 (d, J = 9.0 Hz, 1H), 4.20 (d, J = 31.9 Hz, 2H), 3.66 (d, J = 3.0 Hz, 8H), 2.18 (s, 2H).	483.35
1-(4-(4-氨基-5-(3-甲氧基-4-((4-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,6-二氢吡啶-1(2H)-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.17 (s, 1H), 7.97 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 7.01 - 6.88 (m, 2H), 6.86 - 6.76 (m, 2H), 6.05 (dd, J = 56.6, 19.7 Hz, 3H), 5.68 (d, J = 9.2 Hz, 1H), 4.20 (d, J = 33.4 Hz, 2H), 2.33 (s, 3H), 2.18 (s, 2H).	497.4

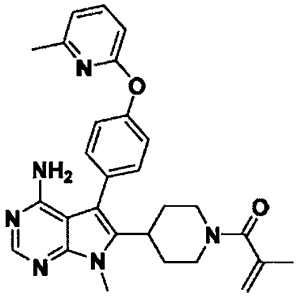
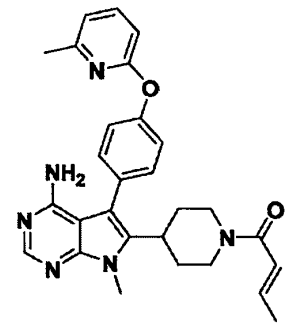
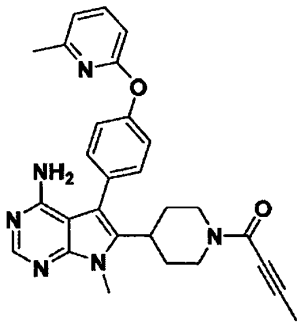
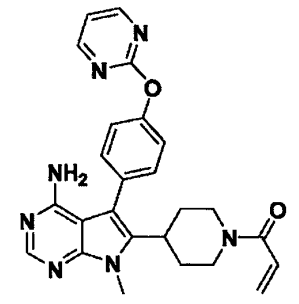
[1308]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-(吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.31 - 8.14 (m, 2H), 7.90 (ddd, J = 9.0, 7.2, 2.0 Hz, 1H), 7.56 - 7.38 (m, 2H), 7.26 - 7.21 (m, 2H), 7.19 (s, 1H), 7.10 (dd, J = 8.3, 2.7 Hz, 1H), 6.50 (ddd, J = 36.0, 16.8, 10.3 Hz, 1H), 6.11 (dt, J = 16.8, 2.7 Hz, 1H), 5.64 (td, J = 9.9, 2.4 Hz, 1H), 4.03 - 3.66 (m, 5H), 3.64 - 3.23 (m, 5H), 2.35 - 1.94 (m, 2H).	441
1-(3-(4-氨基-5-(3-甲氧基-4-(吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.13 (s, 2H), 7.82 (t, J = 8.1 Hz, 1H), 7.27 - 6.94 (m, 5H), 6.64 - 6.37 (m, 1H), 6.11 (d, J = 16.6 Hz, 1H), 5.64 (t, J = 10.5 Hz, 2H), 3.99 - 3.75 (m, 5H), 3.69 (s, 4H), 3.66 - 3.48 (m, 2H), 2.37 - 1.96 (m, 2H).	471.20
1-(3-(4-氨基-5-(3-甲氧基-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.64 (t, J = 4.8 Hz, 2H), 8.14 (s, 1H), 7.37 - 7.19 (m, 2H), 7.12 (s, 1H), 7.01 (dd, J = 7.9, 1.9 Hz, 1H), 4.00 - 3.82 (m, 1H), 3.80 (d, J = 6.4 Hz, 3H), 3.69 (s, 4H), 3.63 (t, J = 10.3 Hz, 1H), 3.33 (s, 1H), 2.35 - 1.95 (m, 2H).	472
1-(3-(4-氨基-5-(3-甲氧基-4-((6-甲基吡啶-3-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.20 (dd, J = 12.7, 2.9 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.32 - 7.17 (m, 2H), 7.17 - 7.04 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 6.60 - 6.38 (m, 1H), 6.10 (dd, J = 16.8, 2.5 Hz, 1H), 5.76 - 5.54 (m, 2H), 3.92 (t, J = 9.1 Hz, 1H), 3.56 (s, 1H), 2.44 (s, 3H), 2.31 - 2.22 (m, 1H), 2.08 (s, 2H).	485.35

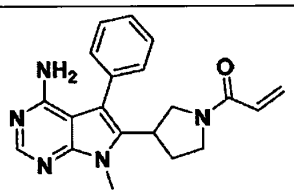
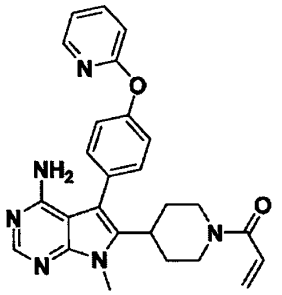
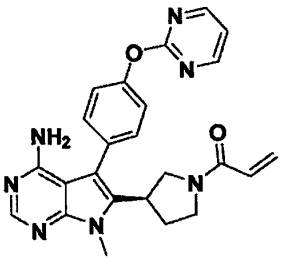
[1309]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丁-2-炔-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 2.1 Hz, 1H), 7.76 (td, J = 7.7, 2.9 Hz, 1H), 7.40 (dd, J = 8.6, 3.3 Hz, 2H), 7.21 (dd, J = 8.1, 5.6 Hz, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.85 (dd, J = 8.2, 2.9 Hz, 1H), 5.78 (s, 1H), 3.92 - 3.65 (m, 5H), 3.50 (dt, J = 18.9, 9.8 Hz, 2H), 3.28 - 3.14 (m, 1H), 2.36 (s, 3H), 2.19 (d, J = 6.9 Hz, 1H), 1.97 (d, J = 19.3 Hz, 4H).	467.25
(E)-1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丁-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.12 (d, J = 2.7 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.41 (dd, J = 8.6, 3.8 Hz, 2H), 7.19 (dd, J = 8.2, 5.7 Hz, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.84 (dd, J = 8.2, 2.6 Hz, 1H), 6.65 (ddt, J = 13.7, 10.7, 6.7 Hz, 1H), 6.17 (ddd, J = 31.7, 14.9, 1.9 Hz, 1H), 5.78 (s, 1H), 3.98 - 3.85 (m, 1H), 3.79 (d, J = 8.4 Hz, 4H), 3.63 (d, J = 9.9 Hz, 1H), 3.53 (d, J = 10.2 Hz, 1H), 3.48 - 3.39 (m, 1H), 2.36 (d, J = 4.2 Hz, 3H), 2.26 - 1.91 (m, 2H), 1.80 (td, J = 6.9, 1.6 Hz, 3H).	469
1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)-2-甲基丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.12 (s, 1H), 7.76 (q, J = 7.5 Hz, 1H), 7.62 - 7.33 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.84 (s, 1H), 5.61(s, 1H), 5.22 (d, J = 18.1 Hz, 1H), 5.05 (d, J = 52.4 Hz, 1H), 3.78 (s, 3H), 3.71 (d, J = 9.5 Hz, 2H), 3.34 (s, 2H), 3.34 (s, 1H), 2.36 (s, 3H), 2.19 (s, 1H), 1.99 (dt, J = 21.1, 10.0 Hz, 1H), 1.81 (d, J = 14.3 Hz, 3H).	469.30

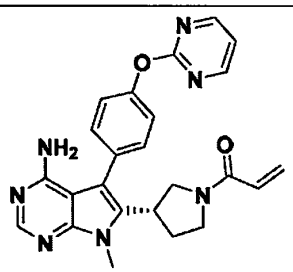
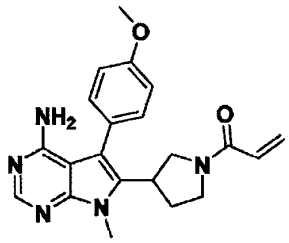
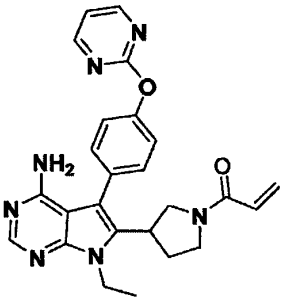
[1310]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基)-2-甲基丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.10 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 5.08 (s, 1H), 4.80 (s, 1H), 4.36 (s, 1H), 3.78 (s, 3H), 3.20 (t, J = 12.4 Hz, 1H), 3.06 (s, 1H), 2.37 (s, 3H), 1.78 (s, 4H), 1.50 (d, J = 10.0 Hz, 2H).	483.35
(E)-1-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基)丁-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.10 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.43 - 7.32 (m, 2H), 7.24 - 7.13 (m, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.63 (dq, J = 13.4, 6.7 Hz, 1H), 6.46 (dd, J = 14.8, 1.9 Hz, 1H), 4.48 (s, 1H), 4.09 (d, J = 13.1 Hz, 1H), 3.77 (s, 3H), 3.16 (t, J = 12.3 Hz, 1H), 3.03 (s, 1H), 2.58 (s, 1H), 2.36 (s, 3H), 1.87 - 1.72 (m, 5H), 1.52 (d, J = 16.1 Hz, 2H).	483.25
1-(4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基)丁-2-炔-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.10 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 8.3 Hz, 2H), 7.31 - 7.15 (m, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 4.39 - 4.20 (m, 2H), 3.78 (s, 3H), 3.23 - 3.07 (m, 2H), 2.66 (dd, J = 13.5, 10.8 Hz, 1H), 2.36 (s, 3H), 2.00 (s, 3H), 1.90 - 1.73 (m, 2H), 1.50 (dtd, J = 37.5, 12.7, 4.2 Hz, 2H).	481.35
1-(4-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J = 4.8 Hz, 2H), 8.14 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.35 - 7.21 (m, 3H), 6.76 (dd, J = 16.7, 10.3 Hz, 1H), 6.17 - 5.90 (m, 1H), 5.63 (d, J = 10.7 Hz, 1H), 4.49 (s, 1H), 4.10 (s, 1H), 3.79 (s, 3H), 2.65 (d, J = 19.5 Hz, 3H), 1.81 (s, 2H), 1.54 (s, 2H).	456

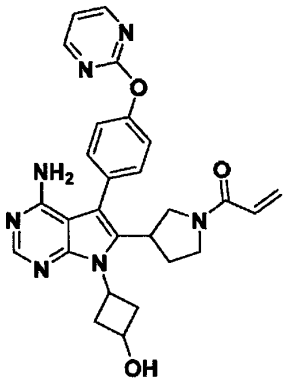
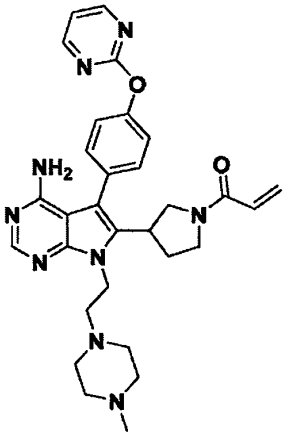
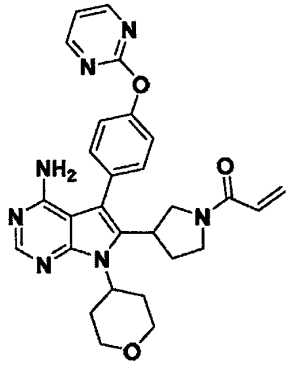
[1311]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-苯基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.9 Hz, 1H), 7.53 - 7.36 (m, 5H), 6.46 (ddd, J = 40.1, 16.8, 10.3 Hz, 1H), 6.08 (ddd, J = 16.8, 4.7, 2.4 Hz, 1H), 5.63 (ddd, J = 12.9, 10.3, 2.5 Hz, 1H), 3.78 (d, J = 6.5 Hz, 4H), 3.66 (s, 1H), 3.50 (s, 2H), 3.25 (s, 1H), 2.31 - 1.71 (m, 2H).	348.15
1-(4-(4-氨基-7-甲基-5-(4-(吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (ddd, J = 4.9, 2.1, 0.8 Hz, 1H), 8.11 (s, 1H), 7.90 (ddd, J = 8.3, 7.2, 2.1 Hz, 1H), 7.42 - 7.34 (m, 2H), 7.25 - 7.15 (m, 3H), 7.07 (dt, J = 8.2, 0.9 Hz, 1H), 6.77 (dd, J = 16.7, 10.5 Hz, 1H), 6.05 (dd, J = 16.7, 2.5 Hz, 1H), 5.63 (dd, J = 10.5, 2.5 Hz, 2H), 4.48 (d, J = 12.7 Hz, 1H), 4.08 (d, J = 13.5 Hz, 1H), 3.78 (s, 3H), 3.23 - 3.12 (m, 1H), 3.06 (t, J = 12.8 Hz, 1H), 2.62 (t, J = 12.6 Hz, 1H), 1.81 (d, J = 12.9 Hz, 2H), 1.58 - 1.48 (m, 2H).	455.25
(R)-1-(3-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (t, J = 4.5 Hz, 2H), 8.15 (d, J = 1.1 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.32 (dd, J = 7.6, 2.9 Hz, 3H), 6.51 (ddd, J = 34.7, 16.8, 10.3 Hz, 1H), 6.11 (ddd, J = 16.8, 5.7, 2.4 Hz, 1H), 5.65 (ddd, J = 12.4, 10.4, 2.5 Hz, 1H), 4.00 - 3.91 (m, 0H), 3.81 (d, J = 6.5 Hz, 3H), 3.78 - 3.45 (m, 3H), 3.34 - 3.24 (m, 0H), 2.22 (tt, J = 10.7, 5.9 Hz, 0H), 2.13 (d, J = 8.3 Hz, 1H), 2.04 (dt, J = 21.0, 11.0 Hz, 0H), 1.24 (s, 1H), 1.18 (t, J = 7.2 Hz, 0H), 0.89 (s, 1H).	442.25

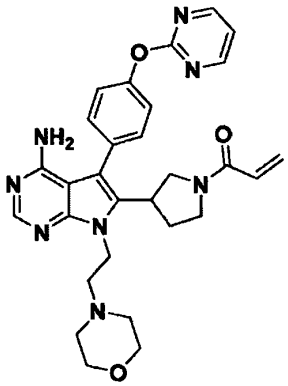
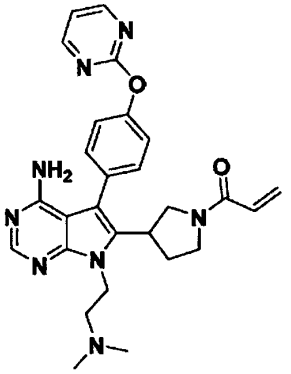
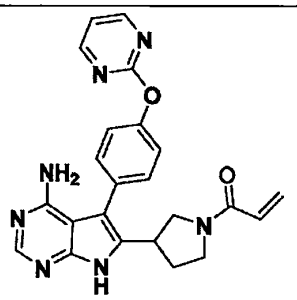
[1312]

化合物	结构	质子 NMR	MS [M+1]
(S)-1-(3-(4-氨基-7-甲基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (t, J = 4.5 Hz, 2H), 8.13 (d, J = 1.8 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.32 (dd, J = 6.5, 3.5 Hz, 3H), 6.51 (ddd, J = 34.2, 16.8, 10.3 Hz, 1H), 6.11 (ddd, J = 16.8, 5.7, 2.4 Hz, 1H), 5.87 (s, 2H), 5.64 (ddd, J = 12.4, 10.4, 2.5 Hz, 1H), 3.80 (d, J = 6.7 Hz, 3H), 3.78 - 3.61 (m, 1H), 3.54 (dtd, J = 24.3, 10.1, 9.6, 6.2 Hz, 1H), 3.34 - 3.24 (m, 0H), 2.28 - 1.94 (m, 2H).	442.25
1-(3-(4-氨基-5-(4-甲氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 1.7 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 6.47 (ddd, J = 40.7, 16.8, 10.3 Hz, 1H), 6.09 (ddd, J = 16.8, 5.6, 2.4 Hz, 1H), 5.63 (ddd, J = 14.6, 10.3, 2.5 Hz, 2H), 3.81 (d, J = 1.1 Hz, 3H), 3.77 (d, J = 6.0 Hz, 4H), 3.66 (q, J = 8.7, 7.2 Hz, 1H), 3.52 (d, J = 9.7 Hz, 2H), 2.35 - 1.70 (m, 2H).	378.15
1-(3-(4-氨基-7-乙基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (t, J = 5.0 Hz, 2H), 8.13 (d, J = 1.6 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.31 (dd, J = 6.0, 3.6 Hz, 3H), 6.49 (ddd, J = 30.9, 16.8, 10.3 Hz, 1H), 6.10 (ddd, J = 16.8, 5.9, 2.5 Hz, 1H), 5.64 (td, J = 10.0, 2.4 Hz, 1H), 4.31 (t, J = 3.2 Hz, 1H), 4.29 (s, 2H), 3.76 (s, 1H), 3.66 (t, J = 9.2 Hz, 1H), 3.61 - 3.51 (m, 1H), 3.49 (t, J = 9.8 Hz, 1H), 3.32 - 3.24 (m, 1H), 2.27 - 2.11 (m, 1H), 2.11 - 1.90 (m, 1H), 1.35 (td, J = 7.0, 3.7 Hz, 3H).	456.3

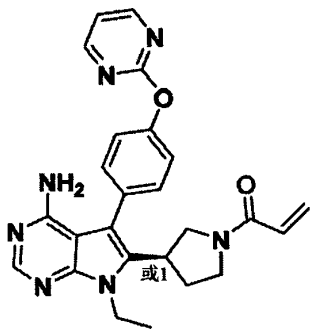
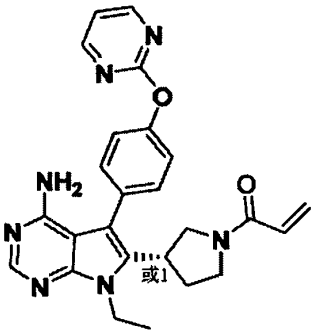
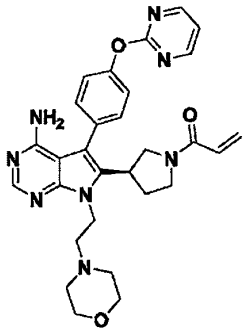
[1313]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-(3-羟基环丁基)-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, 氯仿-d) δ 8.63 (t, J = 3.9 Hz, 2H), 8.26 (d, J = 6.1 Hz, 1H), 7.39 (q, J = 8.9, 8.3 Hz, 4H), 7.14 (t, J = 4.8 Hz, 1H), 6.60 - 6.15 (m, 2H), 5.88 - 5.54 (m, 1H), 4.72 - 4.46 (m, 1H), 4.27 (dd, J = 13.0, 6.6 Hz, 1H), 4.11 - 3.88 (m, 1H), 3.80 (d, J = 8.2 Hz, 1H), 3.59 (tt, J = 19.8, 9.5 Hz, 3H), 3.37 - 2.99 (m, 2H), 2.20 (q, J = 10.3, 9.6 Hz, 2H), 2.05 (d, J = 9.7 Hz, 1H), 1.28 (s, 1H).	498
1-(3-(4-氨基-7-(2-(4-甲基哌嗪-1-基)乙基)-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.62 (t, *J* = 4.8 Hz, 2H), 8.31 (d, *J* = 3.2 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.37 - 7.29 (m, 2H), 7.12 (q, *J* = 4.4 Hz, 1H), 6.43 - 6.33 (m, 1H), 6.28 (dd, *J* = 16.8, 9.8 Hz, 1H), 5.75 - 5.64 (m, 1H), 4.73 (s, 2H), 4.42 (dd, *J* = 14.1, 7.2 Hz, 2H), 3.97 - 3.72 (m, 1H), 3.68 - 3.32 (m, 4H), 2.96 - 2.78 (m, 2H), 2.71 (d, *J* = 24.7 Hz, 8H), 2.41 (d, *J* = 27.9 Hz, 3H), 2.32 - 2.19 (m, 2H), 1.28 (s, 1H).	554.30
1-(3-(4-氨基-5-(4-(嘧啶-2-基氧基)苯基)-7-(四氢-2H-哌喃-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (t, J = 4.5 Hz, 2H), 8.11 (s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.31 (td, J = 6.1, 5.0, 2.0 Hz, 3H), 6.60 (dd, J = 16.8, 10.3 Hz, 1H), 6.13 (ddd, J = 16.7, 8.6, 2.4 Hz, 1H), 5.66 (ddd, J = 19.8, 10.2, 2.4 Hz, 1H), 4.43 (s, 1H), 4.00 (d, J = 11.1 Hz, 2H), 3.80 (s, 2H), 3.72 (s, 0H), 3.57 - 3.48 (m, 2H), 3.51 - 3.38 (m, 1H), 3.38 - 3.25 (m, 1H), 3.04 (d, J = 14.2 Hz, 2H), 2.21 (dd, J = 12.7, 6.6 Hz, 0H), 1.93 (t, J = 10.5 Hz, 0H), 1.74 (d, J = 13.8 Hz, 2H).	512.4

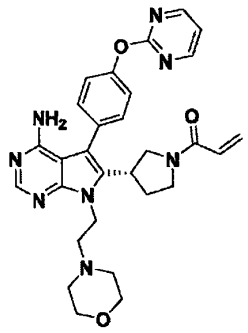
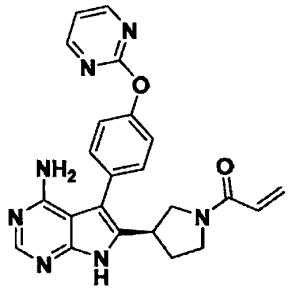
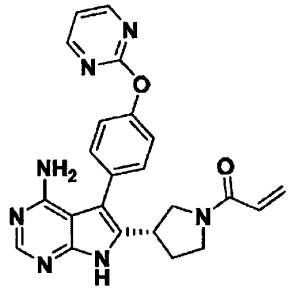
[1314]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-(2-N-吗啉基乙基)-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, J = 5.0 Hz, 2H), 8.12 (s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.8 Hz, 3H), 6.48 (ddd, J = 30.4, 16.8, 10.3 Hz, 1H), 6.16 - 6.05 (m, 1H), 5.88 - 5.31 (m, 2H), 4.35 (q, J = 5.9, 4.8 Hz, 2H), 4.13 - 3.84 (m, 1H), 3.68 (dd, J = 23.6, 9.2 Hz, 2H), 3.64 - 3.44 (m, 6H), 3.34 (s, 2H), 2.72 - 2.50 (m, 4H), 2.40 - 1.47 (m, 2H).	541.45
1-(3-(4-氨基-7-(2-(二甲基氨基)乙基)-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 氯仿-d) δ 8.61 (t, J = 4.6 Hz, 2H), 8.32 (d, J = 2.1 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.36 - 7.30 (m, 2H), 7.12 (td, J = 4.8, 2.4 Hz, 1H), 6.47 - 6.36 (m, 1H), 6.36 - 6.19 (m, 1H), 5.68 (ddd, J = 15.8, 8.6, 3.7 Hz, 1H), 4.70 (s, 2H), 4.41 (dp, J = 21.2, 6.9 Hz, 2H), 4.15 - 3.73 (m, 2H), 3.57 (dtd, J = 39.7, 19.1, 17.7, 8.6 Hz, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.37 (d, J = 10.1 Hz, 6H), 2.31 - 1.98 (m, 2H).	499.25
1-(3-(4-氨基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 4.8 Hz, 2H), 8.10 (s, 1H), 7.47 (dd, J = 8.5, 3.5 Hz, 2H), 7.41 - 7.23 (m, 3H), 6.59 (ddd, J = 16.8, 10.3, 2.4 Hz, 1H), 6.15 (dd, J = 16.8, 2.5 Hz, 1H), 5.67 (ddd, J = 10.7, 8.7, 2.5 Hz, 2H), 4.01 (t, J = 8.9 Hz, 1H), 3.90 - 3.81 (m, 1H), 3.78 - 3.50 (m, 2H), 3.42 (dd, J = 10.7, 6.2 Hz, 1H), 2.42 - 2.03 (m, 2H).	428.25

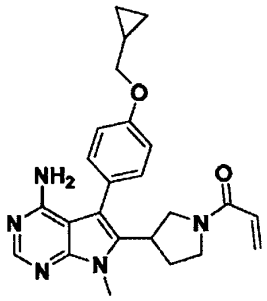
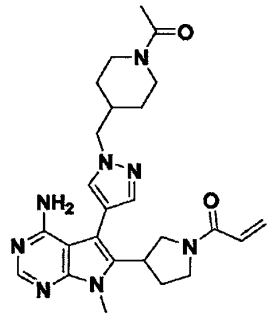
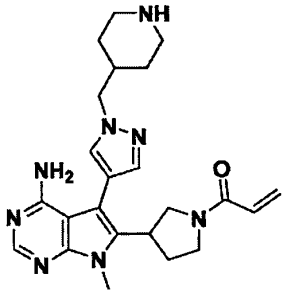
[1315]

化合物	结构	质子 NMR	MS [M+1]
rel-(R)-1-(3-(4-氨基-7-乙基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (t, J = 5.0 Hz, 2H), 8.14 (d, J = 1.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 6.3, 3.9 Hz, 3H), 6.49 (ddd, J = 31.1, 16.8, 10.3 Hz, 1H), 6.10 (ddd, J = 16.9, 5.9, 2.4 Hz, 1H), 5.64 (td, J = 10.0, 2.5 Hz, 1H), 4.30 (d, J = 6.8 Hz, 2H), 3.85 (dd, J = 11.8, 8.0 Hz, 1H), 3.61 - 3.51 (m, 1H), 3.49 (t, J = 9.7 Hz, 1H), 3.27 (d, J = 11.4 Hz, 1H), 2.18 (ddt, J = 26.2, 14.2, 7.0 Hz, 1H), 1.99 - 1.90 (m, 1H), 1.35 (td, J = 7.2, 3.8 Hz, 3H).	456.3
rel-(S)-1-(3-(4-氨基-7-乙基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (t, J = 5.1 Hz, 2H), 8.15 (s, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.31 (td, J = 5.7, 4.9, 2.0 Hz, 3H), 6.49 (ddd, J = 31.5, 16.8, 10.3 Hz, 1H), 6.10 (ddd, J = 16.8, 5.9, 2.4 Hz, 1H), 5.64 (td, J = 10.0, 2.5 Hz, 1H), 4.31 (d, J = 7.5 Hz, 2H), 3.66 (t, J = 9.1 Hz, 2H), 3.51 (dt, J = 19.2, 9.5 Hz, 1H), 2.29 - 2.13 (m, 1H), 2.07 (d, J = 9.5 Hz, 1H), 1.96 (q, J = 10.4 Hz, 1H), 1.35 (td, J = 7.1, 3.5 Hz, 3H).	456.3
(R)-1-(3-(4-氨基-7-(2-N-吗啉基乙基)-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, J = 5.0 Hz, 2H), 8.12 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.31 (dq, J = 7.0, 2.5, 1.9 Hz, 3H), 6.48 (ddd, J = 31.7, 16.8, 10.3 Hz, 1H), 6.10 (ddd, J = 16.8, 5.5, 2.4 Hz, 1H), 5.64 (ddd, J = 10.3, 6.4, 2.4 Hz, 1H), 4.36 (s, 2H), 4.02 - 3.83 (m, 1H), 3.82 - 3.62 (m, 2H), 3.60 - 3.45 (m, 6H), 3.32 (s, 1H), 2.71 - 2.66 (m, 2H), 2.48 (s, 3H), 2.22 (ddt, J = 35.7, 12.7, 6.6 Hz, 1H), 1.99 (dq, J = 44.7, 10.4 Hz, 1H).	541.45

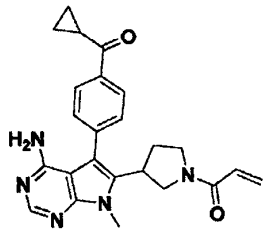
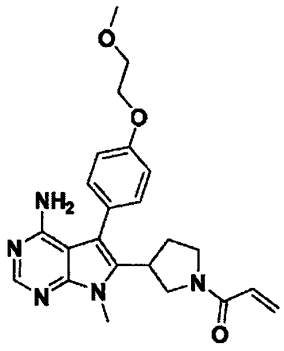
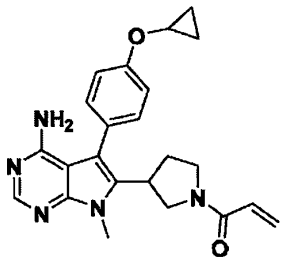
[1316]

化合物	结构	质子 NMR	MS [M+1]
(S)-1-(3-(4-氨基-7-(2-N-吗啉基乙基)-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, J = 5.0 Hz, 2H), 8.12 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 6.1, 3.7 Hz, 3H), 6.48 (ddd, J = 31.6, 16.7, 10.2 Hz, 1H), 6.10 (ddd, J = 16.9, 5.6, 2.5 Hz, 1H), 5.64 (ddd, J = 10.0, 6.6, 2.4 Hz, 1H), 4.37 (d, J = 8.7 Hz, 2H), 4.03 - 3.84 (m, 1H), 3.83 - 3.63 (m, 2H), 3.60 - 3.45 (m, 6H), 3.30 (d, J = 13.6 Hz, 1H), 2.68 (q, J = 6.0, 5.5 Hz, 2H), 2.56 - 2.43 (m, 3H), 2.33 - 2.11 (m, 1H), 1.99 (dq, J = 44.8, 10.6 Hz, 1H).	541.45
(R)-1-(3-(4-氨基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.69 (d, J = 4.8 Hz, 2H), 8.10 (s, 1H), 7.47 (dd, J = 8.5, 3.5 Hz, 2H), 7.39 - 7.19 (m, 3H), 6.59 (ddd, J = 16.8, 10.3, 2.5 Hz, 1H), 6.15 (dd, J = 16.7, 2.5 Hz, 1H), 5.97 - 5.53 (m, 2H), 4.14 - 3.39 (m, 5H), 2.44 - 1.99 (m, 2H).	428.15
(S)-1-(3-(4-氨基-5-(4-(嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.69 (d, J = 4.8 Hz, 2H), 8.11 (s, 1H), 7.47 (dd, J = 8.5, 3.5 Hz, 2H), 7.43 - 7.24 (m, 3H), 6.59 (ddd, J = 16.8, 10.3, 2.5 Hz, 1H), 6.15 (dd, J = 16.8, 2.5 Hz, 1H), 5.67 (ddd, J = 10.7, 8.7, 2.5 Hz, 2H), 4.16 - 3.37 (m, 5H), 2.42 - 2.00 (m, 2H).	428.15

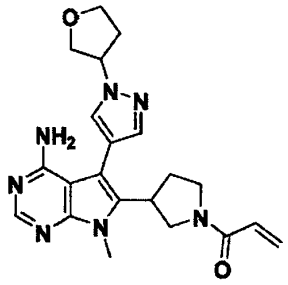
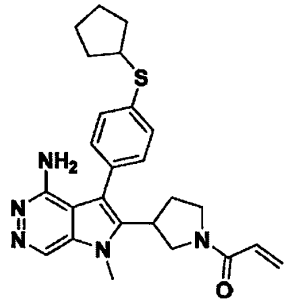
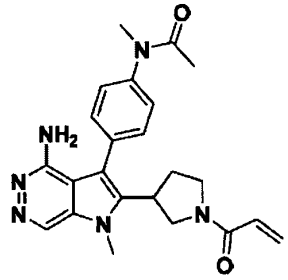
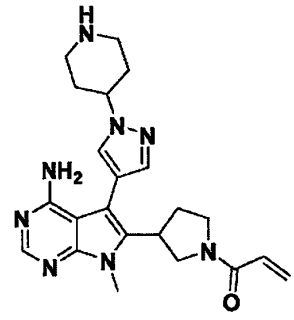
[1317]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(环丙基甲氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 6.47 (ddd, J = 39.8, 16.8, 10.2 Hz, 1H), 6.09 (ddd, J = 16.8, 5.4, 2.5 Hz, 1H), 5.63 (ddd, J = 15.4, 10.3, 2.5 Hz, 1H), 3.89 (dd, J = 17.8, 8.0 Hz, 2H), 3.77 (d, J = 5.8 Hz, 4H), 3.77 - 3.58 (m, 1H), 3.55 - 3.44 (m, 2H), 3.26 (d, J = 10.8 Hz, 1H), 2.00 (dt, J = 45.8, 9.7 Hz, 2H), 1.25 (m, 1H), 0.64 - 0.55 (m, 2H), 0.35 (dd, J = 4.7, 2.3 Hz, 2H).	418.20
1-(3-(5-(1-((1-乙酰基哌啶-4-基)甲基)-1H-吡唑-4-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.09 (d, J = 1.3 Hz, 1H), 7.88 - 7.82 (m, 1H), 7.51 (d, J = 6.1 Hz, 1H), 6.62 - 6.40 (m, 1H), 6.13 (dd, J = 16.7, 2.4 Hz, 1H), 5.71 - 5.61 (m, 2H), 4.34 (d, J = 13.1 Hz, 1H), 4.06 (d, J = 7.4 Hz, 2H), 3.93 (q, J = 9.4 Hz, 0H), 3.76 (d, J = 5.6 Hz, 3H), 3.68 (s, 2H), 3.53 (q, J = 8.1 Hz, 1H), 3.32 (s, 2H), 3.30 (s, 1H), 2.95 (t, J = 13.0 Hz, 1H), 2.47 (d, J = 12.2 Hz, 1H), 2.16 (s, 3H), 1.97 (t, J = 2.2 Hz, 3H), 1.45 (s, 2H), 1.16 - 0.98 (m, 2H).	477.50
1-(3-(4-氨基-7-甲基-5-(1-(哌啶-4-基甲基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 2.6 Hz, 1H), 7.89 - 7.81 (m, 1H), 7.49 (q, J = 3.8 Hz, 1H), 6.47 (ddd, J = 39.8, 16.8, 10.2 Hz, 1H), 6.09 (ddd, J = 16.8, 5.4, 2.5 Hz, 1H), 5.90 (bar, 1H), 5.62 (s, 1H), 4.00 (d, J = 7.6 Hz, 2H), 3.82 - 3.62 (m, 5H), 3.55 - 3.40 (m, 2H), 3.20 (m, 1H), 2.89 (d, J = 11.3 Hz, 1H), 2.79 (s, 1H), 2.36 (d, J = 16.4 Hz, 2H), 2.21 (s, 1H), 2.07 (s, 1H), 1.92 (s, 1H), 1.82 (s, 1H), 1.36 (s, 2H), 1.15 (s, 1H), 1.04 (d, J = 12.9 Hz, 1H).	435.20

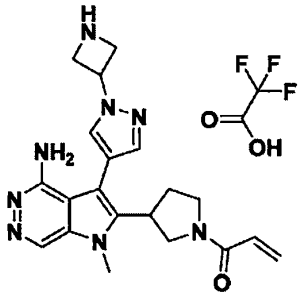
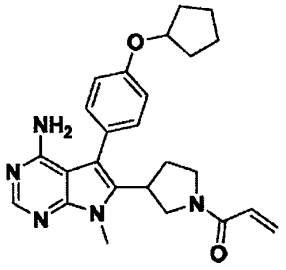
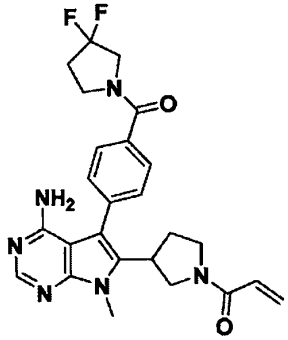
[1318]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(环丙烷羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.17 - 8.10 (m, 3H), 7.55 (d, J = 7.9 Hz, 2H), 6.46 (ddd, J = 38.7, 16.7, 10.3 Hz, 1H), 6.08 (ddd, J = 16.7, 6.1, 2.5 Hz, 1H), 5.61 (ddd, J = 20.0, 10.2, 2.5 Hz, 2H), 4.03 - 3.74 (m, 5H), 3.69 (t, J = 9.0 Hz, 2H), 3.57 (t, J = 9.9 Hz, 1H), 3.00 - 2.92 (m, 1H), 2.28 - 1.84 (m, 2H), 1.07 (d, J = 6.3 Hz, 4H).	416.20
1-(3-(4-氨基-5-(4-(2-甲氧基乙氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 1.6 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 8.2 Hz, 2H), 6.51 -6.42 (dd, J = 16.8, 10.3 Hz, 1H), 6.09 (ddd, J = 16.7, 5.3, 2.4 Hz, 1H), 5.63 (ddd, J = 14.2, 10.3, 2.5 Hz, 2H), 4.18 - 4.11 (m, 2H), 3.97 - 3.88 (m, 4H), 3.77 -3.70 (d, J = 4.6 Hz, 5H), 3.70 - 3.58 (m, 3H), 3.57 - 3.41 (m, 1H), 2.19 (s, 1H), 2.00 (dt, J = 46.6, 9.6 Hz, 1H).	422.20
1-(3-(4-氨基-5-(4-环丙氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) 8.10 (d, J = 1.7 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 6.46 (ddd, J = 45.8, 16.7, 10.2 Hz, 1H), 6.09 (ddd, J = 16.8, 7.0, 2.5 Hz, 1H), 5.79 - 5.51 (m, 2H), 3.89 (dt, J = 6.1, 2.6 Hz, 1H), 3.82 - 3.53 (m, 4H), 3.32 (s, 3H), 3.27 - 3.15 (m, 1H), 2.34 - 1.81 (m, 2H), 1.24 (s, 1H), 0.80 (t, J = 5.7 Hz, 2H), 0.70 (d, J = 3.5 Hz, 2H).	404.20

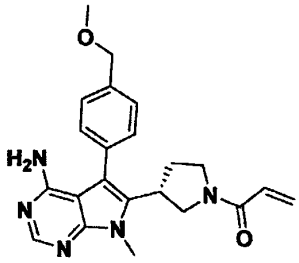
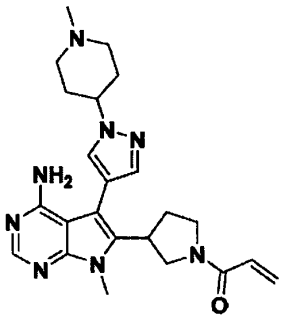
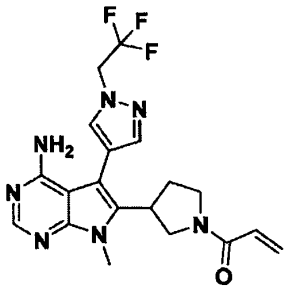
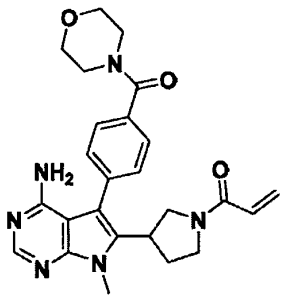
[1319]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(1-(四氢呋喃-3-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 1.5 Hz, 1H), 7.88 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 6.50 (ddd, J = 43.5, 16.8, 10.3 Hz, 1H), 6.11 (dt, J = 16.8, 2.6 Hz, 1H), 5.85 - 5.40 (bar, 2H), 5.64 (td, J = 10.8, 2.5 Hz, 1H), 5.05 (t, J = 5.3 Hz, 1H), 3.98 (ddd, J = 19.1, 10.3, 6.6 Hz, 3H), 3.95 - 3.78 (m, 2H), 3.76 (s, 3H), 3.76 - 3.62 (m, 1H), 3.62 - 3.46 (m, 2H), 3.38 (t, J = 10.1 Hz, 1H), 2.36 (dtd, J = 17.9, 9.2, 8.5, 3.1 Hz, 2H), 2.22 (s, 1H), 2.16 - 1.94 (m, 1H).	408.20
1-(3-{4-氨基-5-[4-(环戊基硫基)苯基]-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.11 (d, J = 1.8 Hz, 1H), 7.43-7.37 (m, 2H), 7.32 (d, J = 7.2 Hz, 2H), 6.52-6.39 (dd, J = 16.8, 10.3 Hz, 1H), 6.09 (ddd, J = 16.8, 6.4, 2.4 Hz, 1H), 5.62 (ddd, J = 18.5, 10.3, 2.5 Hz, 3H), 3.90 (t, J = 9.1 Hz, 1H), 3.81-3.73 (m, 5H), 3.66 (q, J = 10.1, 9.4 Hz, 1H), 3.59-3.52 (m, 1H), 3.48-3.24 (m, 1H), 2.10-1.88 (m, 4H), 1.76-1.52 (m, 6H).	448.19
N-(4-{4-氨基-7-甲基-6-[1-(丙-2-烯酰基)吡咯烷-3-基]-7H-吡咯并[2,3-d]嘧啶-5-基}苯基)-N-甲基乙酰胺		1H NMR (400 MHz, DMSO-d_6) 8.12 (d, J=2.7 Hz, 1H), 7.42 (t, J=6.4 Hz, 4H), 6.45 (ddd, J=49.5, 16.8, 10.3 Hz, 1H), 6.08 (dd, J=16.8, 2.4 Hz, 1H), 5.62 (ddd, J=14.9, 10.3, 2.5 Hz, 3H), 4.17-3.40 (m, 7H), 3.22 (s, 3H), 1.95 (s, 3H), 1.85 (s, 2H).	419.25
1-(3-{4-氨基-7-甲基-5-[1-(哌啶-4-基)-1H-吡唑-4-基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 -8.06 (m, 1H), 7.87 (d, J = 3.0 Hz, 1H), 7.58 -7.46 (m, 1H), 6.65 -6.33 (m, 1H), 6.11 (d, J = 16.8 Hz, 1H) , 5.83 - 5.49 (m, 2H), 4.50 (s, 1H), 4.21 (s, 1H), 3.87 (dt, J = 18.6, 8.5 Hz, 1H), 3.75 (d, J = 7.0 Hz, 5H), 3.64 (dt, J = 17.7, 9.1 Hz, 1H), 3.04 (t, J = 8.0 Hz, 1H), 2.79 (d, J = 13.0 Hz, 2H), 2.38 - 2.06 (m, 3H), 1.97 (d, J = 11.8 Hz, 2H), 1.83 (d, J = 12.1 Hz, 2H).	421.25

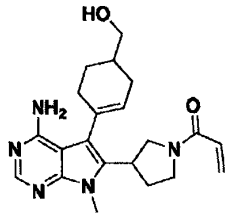
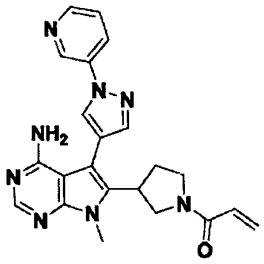
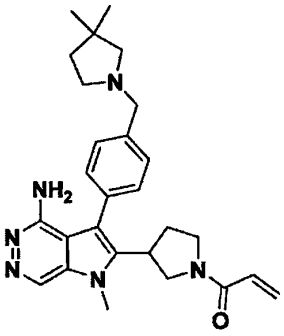
[1320]

化合物	结构	质子 NMR	MS [M+1]
1-(3-{4-氨基-5-[1-(氮杂环丁-3-基)-1H-吡唑-4-基]-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮；三氟乙酸盐		1H NMR (400 MHz, DMSO-d6) 9.10-8.95 (s, 2H), 8.45-8.39 (m,1H), 7.99 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 10.1 Hz, 1H), 6.53-6.41 (dd, J = 16.8, 10.3 Hz, 1H), 6.11 (dd, J = 16.8, 2.4 Hz, 1H), 5.66 (ddd, J = 12.8, 10.2, 2.5 Hz, 1H), 5.41 (td, J = 7.5, 3.7 Hz, 1H), 4.41(m,4H), 3.86 (d, J = 6.2 Hz, 4H), 3.81-3.58 (m, 2H), 3.58-3.33 (dt, J = 12.0, 7.7 Hz, 2H), 2.31-1.93 (m, 2H), 1.08 (s, 1H).	3293.25
1-(3-(4-氨基-5-(4-(环戊基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.10 (d, J = 1.6 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 6.45 (ddd, J = 49.5, 16.8, 10.3 Hz, 1H), 6.08 (ddd, J = 16.8, 7.7, 2.5 Hz, 1H), 5.62 (ddd, J = 19.2, 10.3, 2.5 Hz, 1H), 4.86 (q, J = 4.6, 3.2 Hz, 1H), 3.95 - 3.73 (m, 4H), 3.65 (d, J = 9.8 Hz, 1H), 3.54 - 3.45 (m, 1H), 3.32 (s, 4H), 2.24 - 1.88 (m, 4H), 1.76 (d, J = 12.6 Hz, 4H), 1.60 (d, J = 9.0 Hz, 2H).	*432.35*
1-(3-(4-氨基-5-(4-(3,3-二氟吡咯烷-1-羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.14 (d, *J* = 2.0 Hz, 1H), 7.68 (s, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 6.53 (t, *J* = 13.7 Hz,1H), 6.25 - 6.16 (m, 1H), 5.70 (dd, *J* = 17.9, 10.5 Hz, 1H), 4.04 (s, 2H), 4.02 - 3.91 (m, 6H), 3.88 (d, *J* = 4.8 Hz, 4H), 2.50 (s, 2H), 2.28 (s, 1H), 2.23 - 2.04 (m, 1H).	481.35

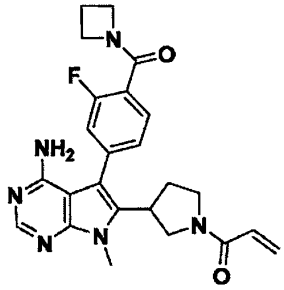
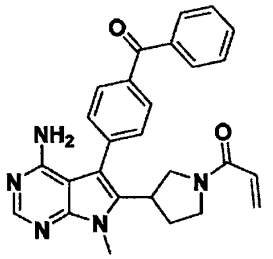
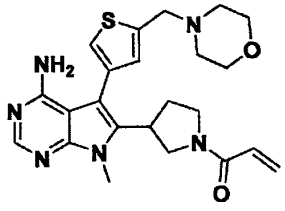
[1321]

化合物	结构	质子 NMR	MS [M+1]
(R)-1-(3-(4-氨基-5-(4-(甲氧基甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 1.9 Hz, 2H), 7.39 (q, J = 7.8 Hz, 8H), 6.51 (dd, J = 16.8, 10.3 Hz, 1H), 6.40 (dd, J = 16.8, 10.3 Hz, 1H), 6.08 (ddd, J = 16.8, 5.7, 2.5 Hz, 2H), 5.62 (ddd, J = 15.9, 10.3, 2.5 Hz, 2H), 4.48 (s, 4H), 3.92 (t, J = 9.1 Hz, 1H), 3.78 (s, 4H), 3.75 - 3.64 (m, 1H), 3.67 - 3.57 (m, 1H), 3.53 (s, 1H), 3.51 (s, 1H), 3.49 - 3.41 (m, 1H), 3.36 - 3.25 (m, 9H), 3.28 - 3.20 (m, 1H), 2.20 (dt, J = 12.5, 6.7 Hz, 1H), 2.15 - 1.89 (m, 2H).	392.10
1-(3-{4-氨基-7-甲基-5-[1-(1-甲基哌啶-4-基)-1H-吡唑-4-基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.11 (s, 1H), 7.84 (d, J = 3.3 Hz, 1H), 7.57 (d, J = 6.3 Hz, 1H), 6.56 - 6.43 (ddd, J = 16.7, 10.4 Hz, 1H), 6.30 - 6.19 (m, 1H), 5.78 - 5.67 (m, 1H), 4.26 (s, 1H), 3.99 - 3.86 (m, 1H), 3.84 (d, J = 2.7 Hz, 4H), 3.75 (d, J = 7.5 Hz, 1H), 3.69 - 3.57 (m, 2H), 3.02 (d, J = 11.4 Hz, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 2.34 - 2.25 (m, 3H), 2.12 (d, J = 12.1 Hz, 2H), 2.05 (s, 1H).	435.20
1-(3-{4-氨基-7-甲基-5-[1-(2,2,2-三氟乙基)-1H-吡唑-4-基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.99 (s, 1H), 7.67 (d, J = 4.6 Hz, 1H), 6.62- 6.36 (m, 1H), 6.12 (ddd, J = 16.7, 4.7, 2.4 Hz, 1H), 5.76 (s, 1), 0 (d, J = 44.9 Hz, 1H), 5.17 (q, J = 9.0 Hz, 2H), 3.93 (t, J = 9.0 Hz, 1H), 3.87 - 3.74 (m, 4H), 3.68 (t, J = 9.1 Hz, 1H), 3.61 - 3.45 (m, 3H), 2.29 - 1.89 (m, 2H).	420.15
1-(3-(4-氨基-7-甲基-5-(4-(吗啉-4-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 3.0 Hz, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 4.8 Hz, 2H), 6.51- 6.42 (dd, J = 16.7, 10.3 Hz, 1H), 6.07 (ddd, J = 16.9, 7.1, 2.4 Hz, 1H), 5.68 - 5.57 (m, 3H), 3.91 (t, J = 9.2 Hz, 4H), 3.79 - 3.31 (d, J = 16.0 Hz, 11H), 3.27 (s, 1H), 2.23 (s, 1H), 2.10 (s, 1H).	461.20

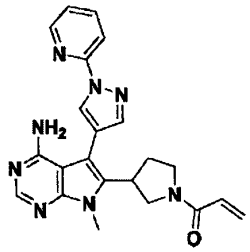
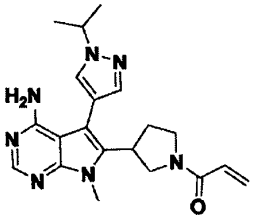
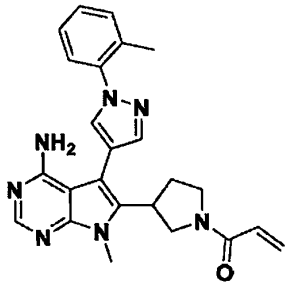
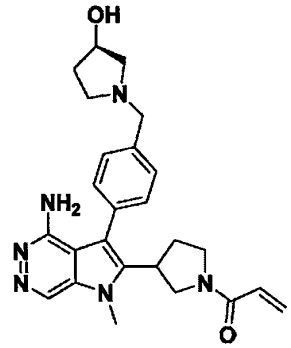
[1322]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(羟基甲基)环己-1-烯-1-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.06 (d, J = 1.3 Hz, 1H), 6.62 (dd, J = 16.8, 10.3 Hz, 1H), 6.01 (s, 3H), 5.76 (s, 2H), 4.52 (t, J = 4.9 Hz, 1H), 4.01 (s, 2H), 3.69 (d, J = 6.0 Hz, 5H), 3.36 (d, J = 5.7 Hz, 2H), 2.21 (s, 5H), 1.87 (s, 3H), 1.40 (s, 1H).	382.40
1-(3-(4-氨基-7-甲基-5-(1-(吡啶-3-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) 9.15 (t, J = 2.5 Hz, 1H), 8.69 (d, J = 11.2 Hz, 1H), 8.54 (dt, J = 4.6, 1.5 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.12 (s, 1H), 7.86 (d, J = 4.0 Hz, 1H), 7.57 (dd, J = 8.4, 4.8 Hz, 1H), 6.48 (ddd, J = 29.3, 16.7, 10.3 Hz, 1H), 6.01 (ddd, J = 16.7, 6.1, 2.5 Hz, 1H), 5.87 (s, 1H), 5.56 (ddd, J = 16.3, 10.3, 2.5 Hz, 1H), 3.94 (t, J = 9.0 Hz, 2H), 3.88 - 3.63 (m, 5H), 3.52 (ddt, J = 29.1, 19.5, 8.3 Hz, 1H), 2.25 (s, 1H), 2.12 (dt, J = 36.2, 10.9 Hz, 1H).	415.40
1-[3-(4-氨基-5-{4-[(3,3-二甲基吡咯烷-1-基)甲基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基]丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.11 (d, J = 2.0 Hz, 1H), 7.36 (ddd, J = 26.6, 8.1, 2.7 Hz, 4H), 6.51-6.37 (dd, J = 16.8, 10.3 Hz, 1H), 6.08 (ddd, J = 16.8, 6.5, 2.5 Hz, 1H), 5.64-5.58 (dd, J = 10.3, 2.5 Hz, 2H), 3.94-3.85 (m, 1H), 3.81-3.69 (m, 4H), 3.69-3.62 (s, 3H), 3.58-3.21 (m, 3H), 3.18 (s, 1H), 2.58 (td, J = 7.0, 3.2 Hz, 2H), 2.29 (d, J = 2.2 Hz, 2H), 2.21-1.88 (m, 2H), 1.54 (t, J = 7.0 Hz, 2H), 1.24 (s, 1H), 1.06 (d, J = 1.4 Hz, 5H).	459.25

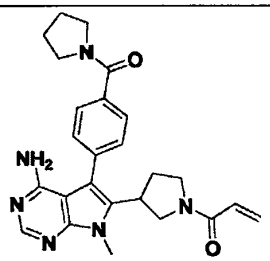
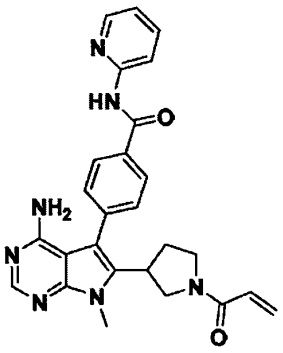
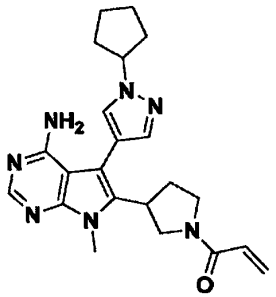
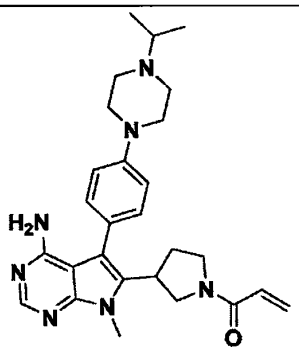
[1323]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(氮杂环丁烷-1-羰基)-3-氟苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 2.6 Hz, 1H), 7.56 (q, J = 7.1 Hz, 1H), 7.30 (ddd, J = 17.0, 10.0, 1.7 Hz, 2H), 6.49 (ddd, J = 29.8, 16.8, 10.4 Hz, 1H), 6.09 (dt, J = 16.8, 3.0 Hz, 1H), 5.64 (td, J = 10.5, 2.4 Hz, 2H), 4.11 - 4.03 (m, 4H), 3.94 (t, J = 9.3 Hz, 1H), 3.82 - 3.66 (m,5H), 3.62 - 3.47 (m, 1H), 2.27 (p, J = 7.6 Hz, 2H), 2.07 (dd, J = 19.2, 9.6 Hz, 1H), 2.03 - 1.91 (m, 1H).	449.25
1-(3-(4-氨基-5-(4-苯甲酰基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 2.4 Hz, 1H), 7.83 (ddd, J = 12.3, 8.9, 6.7 Hz, 4H), 7.71 (t, J = 7.4 Hz, 1H), 7.64 - 7.53 (m, 4H), 6.47 (ddd, J = 38.4, 16.7, 10.3 Hz, 1H), 6.07 (dt, J = 16.8, 2.8 Hz, 1H), 5.90 - 5.33 (bar, 1H), 5.61 (ddd, J = 16.5, 10.3, 2.5 Hz, 1H), 4.00 - 3.68 (m, 6H), 3.65 - 3.54 (m, 1H), 3.54 - 3.37 (m, 1H), 2.24 (s, 1H), 2.18 - 1.97 (m, 1H).	452.15
1-(3-(4-氨基-7-甲基-5-(5-(N-吗啉基甲基)噻吩-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) 8.10 (d, J = 1.7 Hz, 1H), 7.44 (dd, J = 4.5, 1.5 Hz, 1H), 7.00 (d, J = 5.3 Hz, 1H), 6.48 (ddd, J = 50.3, 16.8, 10.3 Hz, 1H), 6.10 (dd, J = 16.7, 2.5 Hz, 2H), 5.80 - 5.50 (m, 2H), 3.92 (t, J = 9.0 Hz, 1H), 3.76 (d, J = 5.7 Hz, 4H), 3.71 (d, J = 4.0 Hz, 3H), 3.58 (t, J = 4.6 Hz, 4H), 3.51 (d, J = 10.1 Hz, 1H), 3.32 (s, 1H), 2.41 (d, J = 5.8 Hz, 4H), 2.32 - 2.11 (m, 1H), 2.10 - 1.89 (m, 1H).	*453.20*

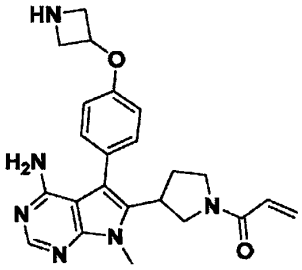
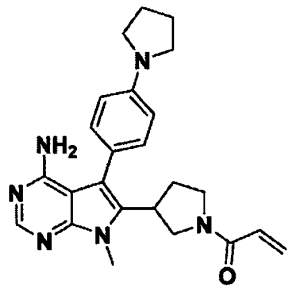
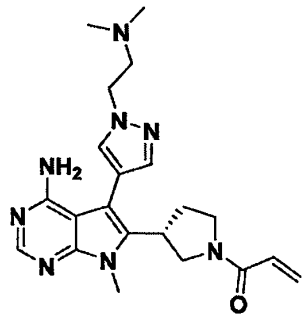
[1324]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(1-(吡啶-2-基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.65 (d, J = 4.4 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 8.07 - 7.95 (m, 2H), 7.88 (d, J = 3.3 Hz, 1H), 7.38 (td, J = 5.5, 4.8, 2.9 Hz, 1H), 6.49 (td, J = 17.4, 10.2 Hz, 1H), 6.04 (dt, J = 16.7, 2.2 Hz, 1H), 5.57 (ddd, J = 15.5, 10.2, 2.5 Hz, 1H), 3.97 (s, 1H), 4.07 - 3.72 (m, 5H), 3.72 - 3.37 (m, 2H), 2.20 - 2.02 (m, 2H).	415.40
1-(3-(4-氨基-5-(1-异丙基-1H-吡唑-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.09 (s, 1H), 7.87 (s, 1H), 7.48 (d, J = 6.5 Hz, 1H), 6.50 (ddd, J = 46.6, 16.8, 10.3 Hz, 1H), 6.11 (ddd, J = 16.8, 4.3, 2.5 Hz, 1H), 5.64 (ddd, J = 12.5, 10.2, 2.5 Hz, 1H), 4.53 (p, J = 6.6 Hz, 1H), 3.89 (t, J = 9.1 Hz, 1H), 3.82 - 3.66 (m, 5H), 3.56 (tq, J = 17.0, 8.9 Hz, 2H), 3.37 (d, J = 10.8 Hz, 0H), 2.26 - 1.93 (m, 2H), 1.44 (d, J = 6.7 Hz, 6H), .	380.25
1-(3-(4-氨基-7-甲基-5-(1-(邻甲苯基)-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.24 - 8.01 (m, 2H), 7.77 (d, J = 8.3 Hz, 1H), 7.54 - 7.27 (m, 3H), 6.51 (ddd, J = 31.5, 16.7, 10.3 Hz, 1H), 6.10 (dt, J = 16.8, 2.2 Hz, 1H), 5.63 (ddd, J = 10.3, 5.7, 2.5 Hz, 2H), 4.00 - 3.67 (m, 4H), 3.65 - 3.39 (m, 3H), 3.33 - 3.17 (m, 2H), 2.34 - 2.00 (m, 5H).	*428.35*
1-{3-[4-氨基-5-(4-{[(3R)-3-羟基吡咯烷-1-基]甲基}苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基]吡咯烷-1-基}丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.11 (d, J=2.0 Hz, 1H), 7.39 (d, J=7.9 Hz, 4H), 6.38 (dd, J=16.8, 10.0 Hz, 1H), 6.08 (ddd, J=16.7, 7.3, 2.5 Hz, 1H), 5.68-5.56 (m, 3H), 4.69 (s, 1H), 4.21 (s, 1H), 3.90-3.42 (t, J=9.0 Hz, 9H), 3.32-3.23 (m, 1H), 2.72 (s, 1H), 2.58 (s, 1H), 2.44 (s, 1H), 2.06-1.89 (m, 3H), 1.56 (s, 1H).	447.25

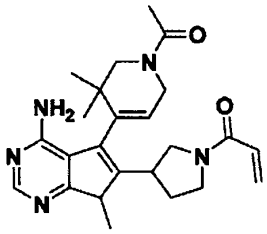
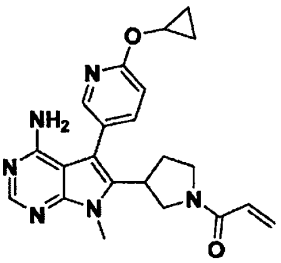
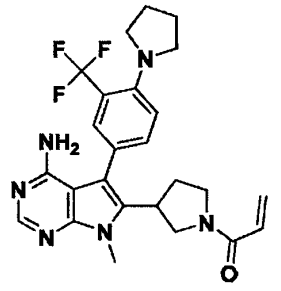
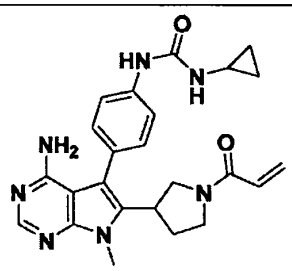
[1325]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.13 (d, J = 2.6 Hz, 1H), 7.60 (t, J = 7.3 Hz, 2H), 7.44 (dd, J = 8.3, 3.3 Hz, 2H), 6.46 (ddd, J = 40.8, 16.8, 10.3 Hz, 1H), 6.07 (dt, J = 16.8, 2.2 Hz, 1H), 5.62 (ddd, J = 14.8, 10.3, 2.5 Hz, 1H), 3.92 (t, J = 9.2 Hz, 1H), 3.79 (d, J = 7.2 Hz, 4H), 3.76 - 3.64 (m, 2H), 3.60 - 3.47 (m, 2H), 3.48 (s, 5H), 3.45 (s, 0H), 2.21 (s, 1H), 2.08 (dd, J = 19.3, 9.4 Hz, 1H), 2.01 - 1.80 (m, 4H).	445.25
4-{4-氨基-7-甲基-6-[1-(丙-2-烯酰基)吡咯烷-3-基]-7H-吡咯并[2,3-d]嘧啶-5-基}-N-(吡啶-2-基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.41 (d, J = 4.9 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.17 -8.08 (m, 3H), 7.91 - 7.82 (m, 1H), 7.53 (d, J = 7.8 Hz, 2H), 7.22 -7.15 (m, 1H), 6.59 - 6.40 (m, 1H), 6.15 -6.05 (m, 1H), 5.63 (t, J = 11.4 Hz, 2H), 3.81 (d, J = 7.0 Hz, 6H), 3.57 (t, J = 9.6 Hz, 2H), 2.21 (s, 1H), 2.10 (d, J = 12.5 Hz, 1H).	468.20
1-(3-(4-氨基-5-(1-环戊基-1H-吡唑-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 1.4 Hz, 1H), 7.87 (s, 1H), 7.48 (d, J = 6.2 Hz, 1H), 6.50 (ddd, J = 46.7, 16.8, 10.3 Hz, 1H), 6.11 (ddd, J = 16.8, 4.0, 2.5 Hz, 1H), 5.64 (ddd, J = 12.5, 10.2, 2.5 Hz, 1H), 4.73 (p, J = 6.7 Hz, 2H), 3.93 - 3.46 (m, 8H), 2.28 - 1.50 (m, 10H).	406.30
1-[3-(4-氨基-7-甲基-5-{4-[4-(丙-2-基)哌嗪-1-基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基]丙-2-烯-1-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.11 (s, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.08 (s, 2H), 6.36 - 6.23 (m, 1H), 6.23- 6.14 (m, 1H), 5.76-5.61 (m, 1H), 3.84 (s, 5H), 3.68 (s, 2H), 3.61 (s, 2H), 3.59- 3.39 (m, 2H), 3.32 (d, J = 1.7 Hz, 1H), 2.80 (s, 5H), 2.34 - 1.97 (m, 2H), 1.18 (d, J = 6.5 Hz, 6H).	474.45

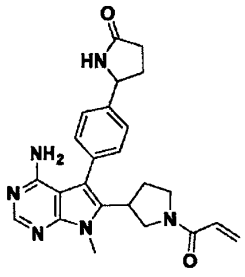
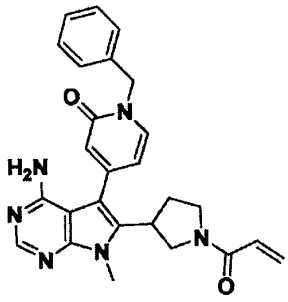
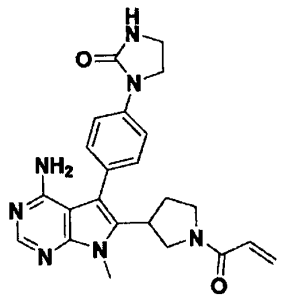
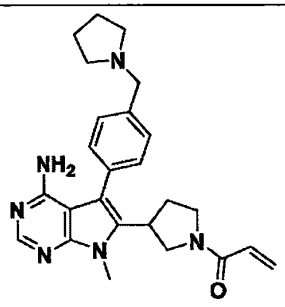
[1326]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(氮杂环丁-3-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.12 (d, J = 7.3 Hz, 1H), 7.57 (dd, J = 8.1, 2.3 Hz, 1H), 7.50 (dd, J = 8.2, 2.4 Hz, 1H), 7.27 - 7.20 (m, 1H), 7.04 (ddd, J = 8.0, 5.5, 2.6 Hz, 1H), 4.99 (dt, J = 21.0, 6.5 Hz, 1H), 4.12 - 4.00 (m, 1H), 3.84 (d, J = 1.1 Hz, 3H), 3.68 (dd, J = 9.6, 6.4 Hz, 1H), 3.64 - 3.57 (m, 1H), 3.51 (t, J = 6.9 Hz, 3H), 3.43 (q, J = 7.2 Hz,2H), 3.24 - 3.05 (m, 1H), 2.56 - 2.38 (m, 2H), 2.17 - 1.84 (m, 3H).	419.30
1-(3-{4-氨基-7-甲基-5-[4-(吡咯烷-1-基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.21 (s, 1H), 8.11 (d, J = 1.4 Hz, 1H), 7.23 - 7.14 (m, 2H), 6.71 - 6.63 (m, 2H), 6.52 (dd, J = 16.8, 10.4 Hz, 1H), 6.36 - 6.10 (m, 1H), 5.66 (ddd, J = 37.9, 10.4, 2.1 Hz, 1H), 3.85 (s, 5H), 3.82 - 3.62 (m, 2H), 3.66 -3.45 (dd, J = 12.3, 7.8 Hz, 4H), 3.36 (s, 1H), 2.28 (s, 2H), 2.07 (td, J = 7.5, 6.3, 4.2 Hz, 5H).	417.20
(R)-1-(3-(4-氨基-5-(1-(2-(二甲基氨基)乙基)-1H-吡唑-4-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 1.6 Hz, 1H), 7.82 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 6.52 (ddd, J = 35.3, 16.7, 10.3 Hz, 1H), 6.12 (dt, J = 16.8, 2.1 Hz, 1H), 5.65 (td, J = 10.2, 2.5 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.93 (t, J = 8.9 Hz, 1H), 3.84 - 3.61 (m, 5H), 3.61 - 3.45 (m, 1H), 3.40 - 3.29 (m, 0H), 2.61 (t, J = 6.2 Hz, 2H), 2.14 (d, J = 1.7 Hz, 8H).	409.25

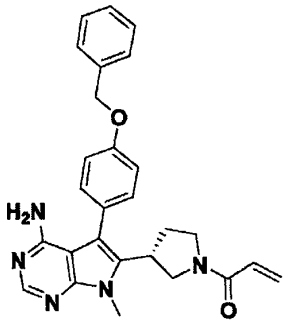
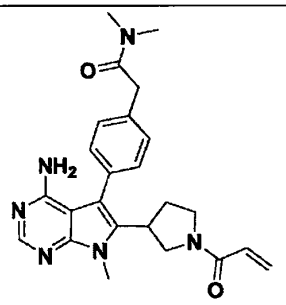
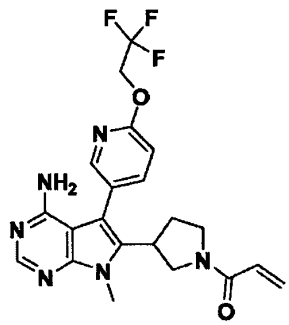
[1327]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(5-(1-乙酰基-3,3-二甲基-1,2,3,6-四氢吡啶-4-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.08 (s, 1H), 7.35 - 7.26 (m, 1H), 6.61 (ddd, J = 15.4, 7.8, 3.3 Hz, 1H), 6.44 (d, J = 12.0 Hz, 1H), 6.12 (dt, J = 15.7, 3.6 Hz, 1H), 4.23 - 4.07 (dd, J = 11.4, 6.4 Hz, 3H), 3.92 - 3.79 (m, 1H), 3.78 (d, J = 3.7 Hz, 4H), 3.73 (s, 1H), 3.71 - 3.60 (m, 1H), 3.44 (dd, J = 19.4, 4.4 Hz, 2H), 2.59 - 2.40 (dd, J = 12.0, 6.0 Hz, 1H), 2.28 - 2.06 (m, 1H), 2.16 (dd, J = 6.0, 4.1 Hz, 3H), 1.16 (dd, J = 19.4, 4.7 Hz, 6H).	423.20
1-(3-(4-氨基-5-(6-环丙氧基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) 8.20 (dd, J = 5.9, 2.4 Hz, 1H), 8.13 (s, 1H), 7.71 (dt, J = 8.4, 2.3 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.47 (ddd, J = 38.4, 16.7, 10.2 Hz, 1H), 6.09 (dt, J = 16.8, 2.8 Hz, 1H), 5.63 (ddd, J = 13.1, 10.2, 2.5 Hz, 3H), 4.25 (td, J = 6.1, 3.4 Hz, 1H), 3.81 - 3.59 (m, 5H), 3.51 (m, 2H), 3.26 (s, 1H), 2.28 - 1.59 (m, 2H), 0.90 - 0.57 (m, 4H).	*405.25*
1-(3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-基)-3-(三氟甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.5 Hz, 1H), 7.58 - 7.30 (m, 2H), 7.11 (d, J = 8.6 Hz, 1H), 6.73 - 6.25 (m, 1H), 6.08 (ddd, J = 16.8, 9.1, 2.5 Hz, 1H), 5.62 (ddd, J = 20.0, 10.3, 2.3 Hz, 3H), 3.77 (d, J = 5.8 Hz, 4H), 3.65 (q, J = 8.8 Hz, 1H), 3.51 (dt, J = 21.3, 9.3 Hz, 1H), 3.36 (s, 4H), 2.39 - 1.96 (m, 2H), 1.92 (d, J = 6.0 Hz, 5H).	485.35
1-(4-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)-3-环丙基脲		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.10 (d, J = 1.7 Hz, 1H), 7.57 - 7.44 (m, 2H), 7.23 (d, J = 8.2 Hz, 2H), 6.59 - 6.37 (m, 2H), 6.09 (ddd, J = 16.8, 4.2, 2.5 Hz, 1H), 5.63 (ddd, J = 13.1, 10.3, 2.5 Hz, 1H), 3.96 - 3.38 (m, 8H), 2.56 (dt, J = 7.1, 3.5 Hz, 1H), 2.31 - 1.94 (m, 2H), 0.65 (td, J = 6.9, 4.7 Hz, 2H), 0.47 - 0.38 (m, 2H).	446.35

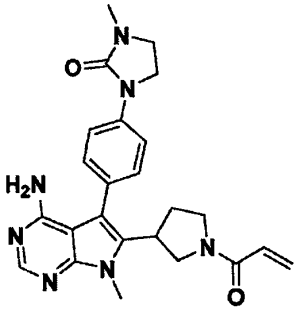
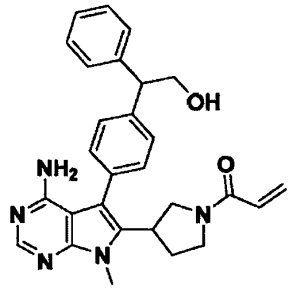
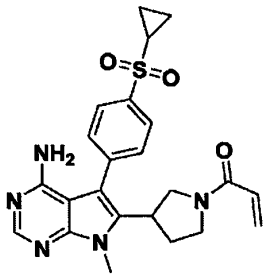
[1328]

化合物	结构	质子 NMR	MS [M+1]
5-(4-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (t, J = 2.9 Hz, 2H), 7.39 (d, J = 2.5 Hz, 4H), 6.62 - 6.28 (m, 1H), 6.14 - 6.04 (m, 1H), 5.63 (ddd, J = 14.3, 10.2, 2.4 Hz, 2H), 4.75 (t, J = 7.0 Hz, 1H), 3.91 (t, J = 9.2 Hz, 1H), 3.79 (d, J = 6.8 Hz, 3H), 3.74 (s, 2H), 3.66 (d, J = 9.8 Hz, 1H), 3.54 (s, 1H), 2.30 - 2.20 (m, 2H), 2.20 (s, 1H), 2.09 (d, J = 8.3 Hz, 1H), 2.03 - 1.69 (m, 3H).	431.25
4-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-1-苯甲基吡啶-2(1H)-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.16 (d, J = 1.0 Hz, 1H), 7.78 (dd, J = 11.1, 6.8 Hz, 1H), 7.45 - 7.35 (m, 4H), 7.39 - 7.29 (m, 1H), 6.65 - 6.42 (m, 3H), 6.31 - 6.20 (m, 1H), 5.72 (ddd, J = 22.8, 10.4, 2.0 Hz, 1H), 5.25 (s, 2H), 4.08 - 3.43 (m, 8H), 2.44 - 2.18 (m, 2H).	455.35
1-(4-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)咪唑啶-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.02 (s, 1H), 6.48 (ddd, J = 33.0, 16.7, 10.3 Hz, 1H), 6.14 - 6.04 (m, 1H), 5.68 - 5.57 (m, 2H), 3.92 (dt, J = 15.5, 8.6 Hz, 2H), 3.78 (d, J = 6.3 Hz, 4H), 3.50 (s, 3H), 3.43 (t, J = 8.1 Hz, 2H), 3.27 (s, 1H), 2.20 (d, J = 12.5 Hz, 1H), 2.06 (s, 1H).	432.25
1-(3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-基甲基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.1 Hz, 1H), 7.36 (ddd, J = 28.1, 7.8, 4.0 Hz, 4H), 6.66 - 6.22 (m, 1H), 6.08 (ddd, J = 16.9, 6.5, 2.4 Hz, 1H), 5.61 (ddd, J = 20.5, 10.3, 2.5 Hz, 1H), 3.81 - 3.71 (m, 4H), 3.68 - 3.63 (m, 1H), 3.63 (s, 2H), 3.59 - 3.42 (m, 1H), 3.26 (dd, J = 19.8, 9.4 Hz, 1H), 2.46 (s, 5H), 2.21 (s, 1H), 2.16 - 1.97 (m, 1H), 1.72 (d, J = 6.0 Hz, 4H).	431.50

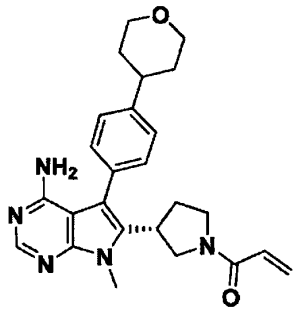
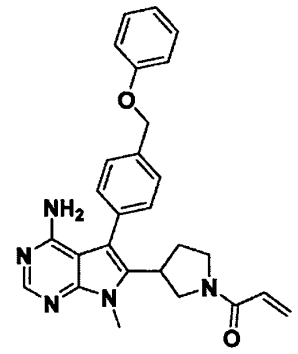
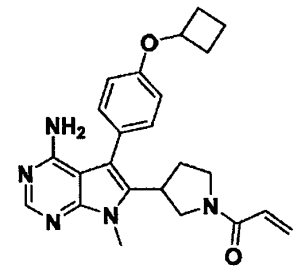
[1329]

化合物	结构	质子 NMR	MS [M+1]
(R)-1-(3-(4-氨基-5-(4-(苯甲氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.6 Hz, 1H), 7.54 - 7.28 (m, 7H), 7.11 (d, J = 8.0 Hz, 2H), 6.52 (dd, J = 16.8, 10.3 Hz, 1H), 6.10 (ddd, J = 16.8, 5.7, 2.4 Hz, 1H), 5.63 (ddd, J = 15.0, 10.3, 2.5 Hz, 1H), 5.14 (s, 2H), 3.97 - 3.88 (m, 0H), 3.77 (d, J = 5.9 Hz, 4H), 3.70 - 3.58 (m, 1H), 3.57 - 3.40 (m, 1H), 3.27 (s, 1H), 2.26 - 1.87 (m, 2H).	454.35
2-(4-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)-N,N-二甲基乙酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 2.5 Hz, 4H), 6.45 (dd, J = 41.8, 10.3 Hz, 1H), 6.09 (ddd, J = 16.7, 6.1, 2.4 Hz, 1H), 5.63 (ddd, J = 13.5, 10.3, 2.5 Hz, 1H), 3.92 (t, J = 9.2 Hz, 1H), 3.81 - 3.74 (m, 6H), 3.72 - 3.63 (m, 1H), 3.51 (dd, J = 20.4, 10.0 Hz, 1H), 3.03 (s, 3H), 2.99 (s, 1H), 2.86 (s, 3H), 2.20 (d, J = 7.3 Hz, 1H), 2.09 (t, J = 10.3 Hz, 1H).	433.25
1-(3-(4-氨基-7-甲基-5-(6-(2,2,2-三氟乙氧基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (t, J = 2.9 Hz, 1H), 8.12 (d, J = 1.5 Hz, 1H), 7.80 (dd, J = 8.3, 2.9 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.51 - 6.41 (dd, J = 16.7, 10.2 Hz, 1H), 6.09 (dt, J = 16.9, 3.1 Hz, 1H), 5.80 - 5.50 (bar, 2H), 5.63 (ddd, J = 15.3, 10.2, 2.5 Hz, 1H), 5.01 (q, J = 9.1 Hz, 2H), 3.93 (t, J = 9.1 Hz, 1H), 3.79 (d, J = 6.8 Hz, 4H), 3.67 (s, 1H), 3.56 - 3.43 (m, 1H), 3.31 - 3.22 (m, 1H), 2.25 - 1.89 (m, 2H).	447.10

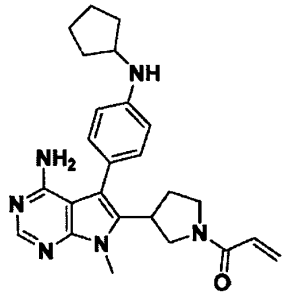
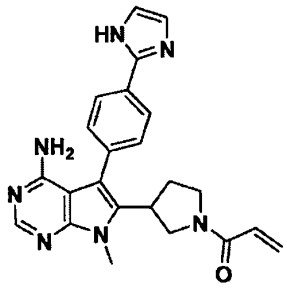
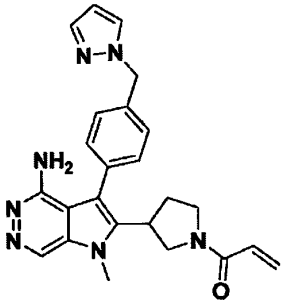
[1330]

化合物	结构	质子 NMR	MS [M+1]
1-(4-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)-3-甲基咪唑啶-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.8 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.48 (ddd, J = 33.2, 16.8, 10.3 Hz, 1H), 6.09 (ddd, J = 16.8, 5.4, 2.5 Hz, 1H), 5.62 (ddd, J = 14.2, 10.3, 2.5 Hz, 1H), 3.94 (t, J = 9.0 Hz, 1H), 3.80 (dd, J = 21.6, 7.2 Hz, 5H), 3.65 (tt, J = 18.0, 8.7 Hz, 1H), 3.57 - 3.42 (m, 2H), 3.30 - 3.15 (m, 1H), 2.79 (s, 3H), 2.24 - 2.17 (m, 1H), 2.12 - 1.91 (m, 1H).	446.30
1-(3-(4-氨基-5-(4-(2-羟基-1-苯基乙基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 2.7 Hz, 1H), 7.41 - 7.35 (m, 2H), 7.34 - 7.26 (m, 6H), 7.20 (tt, J = 5.6, 2.8 Hz, 1H), 6.51 - 6.37 (ddd, J = 16.9, 10.3, 3.9 Hz, 1H), 6.08 (ddd, J = 16.8, 13.8, 2.3 Hz, 1H), 5.69 - 5.52 (ddd, J = 10.3, 4.6, 2.4 Hz, 1H), 4.81 (t, J = 5.3 Hz, 1H), 4.16 (t, J = 7.2 Hz, 1H), 4.08 - 3.94 (m, 2H), 3.80 - 3.68 (m, 4H), 3.66 - 3.41 (m, 3H), 3.24 (dd, J = 11.9, 8.0 Hz, 1H), 2.18 - 1.91 (t, J = 10.7 Hz, 2H).	468.20
1-(3-(4-氨基-5-(4-(环丙基磺酰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 8.4, 2.9 Hz, 2H), 7.65 (d, J = 7.9 Hz, 2H), 6.59 - 6.40 (dd, J = 16.8, 10.3 Hz, 1H), 6.10 (ddd, J = 16.8, 4.0, 2.5 Hz, 1H), 5.64 (ddd, J = 14.4, 10.2, 2.4 Hz, 1H), 3.94 - 3.72 (m, 3H), 3.71 - 3.55 (m, 3H), 3.55 - 3.44 (m, 1H), 3.27 (s, 1H), 2.96 - 2.87 (m, 1H), 2.21 (d, J = 6.7 Hz, 1H), 2.12 (t, J = 10.3 Hz, 1H), 1.27 - 1.15 (m, 2H), 1.09 (dt, J = 8.2, 2.7 Hz, 2H).	452.15

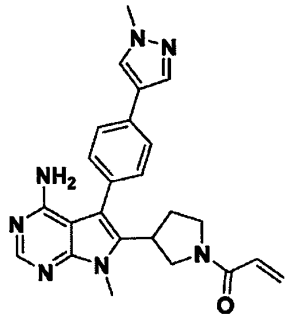
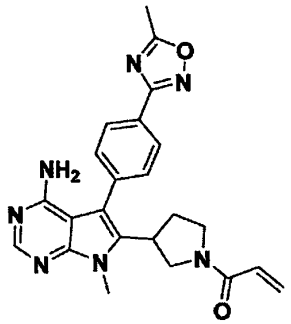
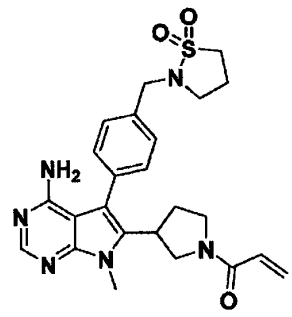
[1331]

化合物	结构	质子 NMR	MS [M+1]
(R)-1-(3-(4-氨基-7-甲基-5-(4-(四氢-2H-哌喃-4-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.0 Hz, 1H), 7.35 (q, J = 7.3, 6.7 Hz, 4H), 6.51 (dd, J = 16.8, 10.3 Hz, 1H), 6.38 (dd, J = 16.8, 10.3 Hz, 0H), 6.08 (ddd, J = 16.8, 10.2, 2.5 Hz, 1H), 5.62 (ddd, J = 20.1, 10.2, 2.5 Hz, 1H), 4.01 - 3.93 (m, 2H), 3.93 - 3.84 (m, 1H), 3.79 (s, 2H), 3.77 (s, 2H), 3.76 - 3.59 (m, 1H), 3.58 - 3.44 (m, 2H), 3.43 (d, J = 2.8 Hz, 1H), 3.36 - 3.21 (m, 1H), 2.89 - 2.79 (m, 1H), 2.10 (s, 1H), 2.08 (s, 1H), 1.97 (p, J = 10.9, 10.3 Hz, 1H), 1.72 (dq, J = 16.5, 12.6 Hz, 4H).	432.35
1-(3-{4-氨基-7-甲基-5-[4-(苯氧基甲基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.47 (ddd, J = 37.4, 16.8, 10.3 Hz, 1H), 6.09 (ddd, J = 16.6, 7.2, 2.4 Hz, 1H), 5.63 (ddd, J = 15.7, 10.1, 2.5 Hz, 1H), 5.17 (s, 2H), 3.94 (t, J = 9.2 Hz, 1H), 3.79 (d, J = 6.2 Hz, 4H), 3.66 (q, J = 9.3 Hz, 1H), 3.60 - 3.42 (m, 2H), 3.28 (d, J = 11.6 Hz, 1H), 2.08 (s, 4H), 1.16 (dt, J = 26.1, 13.1 Hz, 1H).	454.20
1-(3-(4-氨基-5-(4-环丁氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.10 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H), 6.46 (ddd, J = 46.5, 16.8, 10.3 Hz, 1H), 6.09 (ddd, J = 16.8, 7.0, 2.5 Hz, 1H), 5.83 - 4.98 (m, 2H), 4.72 (q, J = 7.1 Hz, 1H), 3.93 - 3.60 (m, 5H), 3.32 (s, 3H), 3.31 - 3.23 (m, 1H), 2.48 - 2.00 (m, 5H), 1.87 - 1.60 (m, 2H).	418.25

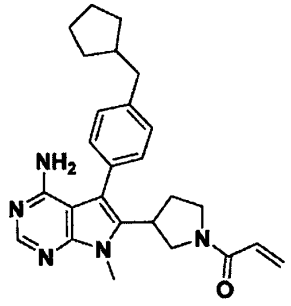
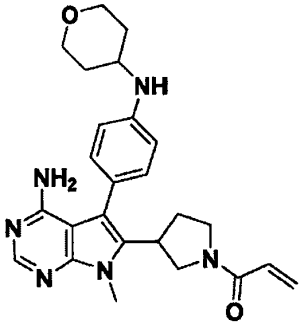
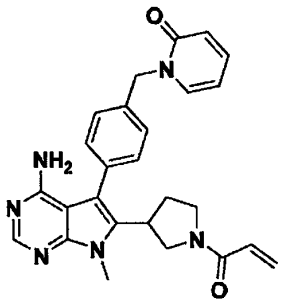
[1332]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(环戊基氨基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 1.8 Hz, 1H), 7.05 (d, J = 7.7 Hz, 2H), 6.63 (d, J = 8.0 Hz, 2H), 6.48 (ddd, J = 41.0, 16.7, 10.3 Hz, 1H), 6.09 (ddd, J = 16.8, 7.6, 2.4 Hz, 1H), 5.83 - 5.76 (m, 1H), 5.62 (ddd, J = 17.7, 10.2, 2.5 Hz, 1H), 3.95 - 3.70 (m, 6H), 3.70 - 3.42 (m, 1H), 3.28 (d, J = 10.9 Hz, 1H), 2.25 - 1.85 (m, 4H), 1.72 - 1.67 (m, 2H), 1.60 - 1.44 (m, 4H), 1.29 - 0.99 (m, 1H).	431.35
1-(3-(5-(4-(1H-咪唑-2-基)苯基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 2.0 Hz, 1H), 7.07 (s, 1H), 6.47 (ddd, J = 27.8, 16.8, 10.3 Hz, 1H), 6.07 (ddd, J = 16.8, 5.9, 2.5 Hz, 1H), 5.60 (ddd, J = 19.1, 10.3, 2.5 Hz, 2H), 3.97 (t, J = 9.3 Hz, 0H), 3.80 (d, J = 6.6 Hz, 4H), 3.68 (d, J = 9.0 Hz, 1H), 3.60 - 3.49 (m, 2H), 2.04 (dq, J = 33.4, 11.2 Hz, 2H).	414.15
1-[3-(4-氨基-7-甲基-5-{4-[(1H-吡唑-1-基)甲基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基]丙-2-烯-1-酮		1H NMR (400 MHz, 甲醇-d4) 8.14 (d, J = 0.8 Hz, 1H), 7.80 (d, J = 2.3 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.46-7.38 (m, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.50 (dd, J = 16.8, 10.4 Hz, 1H), 6.39 (t, J = 2.2 Hz, 1H), 6.32-6.21 (td, J = 16.4, 2.1 Hz, 2H), 5.73-5.66 (dd, J = 10.3, 2.2 Hz, 1H), 5.51 (s, 1H), 5.45 (d, J = 2.6 Hz, 2H), 3.98-3.75 (m, 5H), 3.78-3.35 (m, 3H), 2.35-2.05 (s, 2H).	428.25

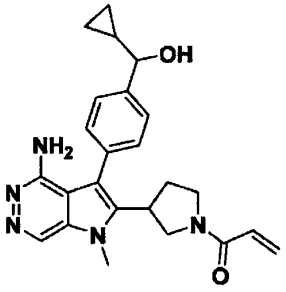
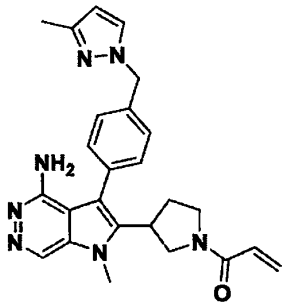
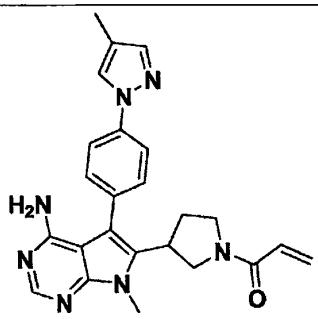
[1333]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-(1-甲基-1H-吡唑-4-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.92 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 6.51- 6.43 (dd, J = 16.8, 10.3 Hz, 1H), 6.07 (ddd, J = 16.7, 8.1, 2.5 Hz, 1H), 5.61 (ddd, J = 20.9, 10.3, 2.4 Hz, 2H), 3.95 (t, J = 9.2 Hz, 0H), 3.89 (s, 3H), 3.79 (d, J = 6.2 Hz,4H), 3.67 (q, J = 12.0, 10.8 Hz, 1H), 3.56 (t, J = 10.1 Hz, 2H), 3.54 - 3.27 (d, J = 8.1 Hz, 1H), 2.25- 1.95 (m, 1H).	428.15
1-(3-(4-氨基-7-甲基-5-(4-(5-甲基-1,2,4-恶二唑-3-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 1.7 Hz, 1H), 8.07 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 6.51 -6.42 (dd, J = 16.7, 10.3 Hz, 1H), 6.06 (ddd, J = 16.8, 7.1, 2.4 Hz, 1H), 5.63 (dd, J = 10.3, 2.5 Hz, 1H), 5.57 (dd, J = 10.2, 2.5 Hz, 1H), 3.99 - 3.90 (m, 1H), 3.81 (d, J = 6.6 Hz, 5H), 3.69 (d, J = 8.6 Hz, 1H), 3.58 (d, J = 9.8 Hz, 1H), 3.50 - 3.28 (d, J = 10.1 Hz, 1H), 2.70 (s, 3H), 2.26 - 2.19 (m, 1H), 2.11 - 1.94 (m, 1H).	430.15
1-(3-(4-氨基-5-(4-((1,1-二氧离子基异噻唑啶-2-基)甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) 8.12 (d, J = 2.2 Hz, 1H), 7.53 - 7.30 (m, 4H), 6.45 (ddd, J = 46.4, 16.7, 10.3 Hz, 1H), 6.08 (dt, J = 16.7, 2.4 Hz, 1H), 5.62 (ddd, J = 15.1, 10.2, 2.4 Hz, 1H), 5.58 - 4.92 (s, 1H),4.23 - 4.09 (m, 2H), 4.00 - 3.72 (m, 4H), 3.70 - 3.35 (m, 2H), 3.33 (s, 1H), 3.28 (t, J = 7.7 Hz, 3H), 3.14 (td, J = 6.8, 2.3 Hz, 2H), 2.24 (p, J = 7.0 Hz, 3H), 2.09 (dt, J = 14.1, 8.2 Hz, 1H), 1.96 (dq, J = 21.2, 10.5 Hz, 1H).	481.25

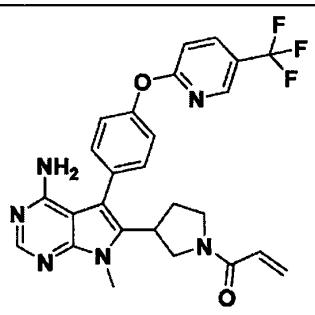
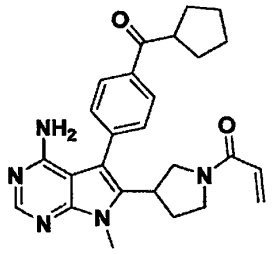
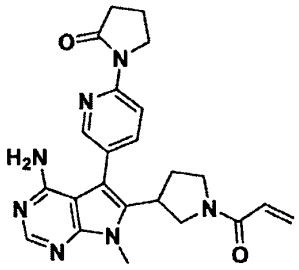
[1334]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(环戊基甲基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 2.6 Hz, 4H), 6.44 (ddd, J = 55.7, 16.7, 10.3 Hz, 1H), 6.08 (ddd, J = 16.7, 7.0, 2.4 Hz, 1H), 5.61 (ddd, J = 20.9, 10.2, 2.5 Hz, 2H), 3.92 - 3.73 (m, 4H), 3.64 (t, J = 9.1 Hz, 1H), 3.58 - 3.38 (m, 2H), 3.29 - 3.22 (m, 1H), 2.64 (d, J = 7.5 Hz, 2H), 2.28 - 1.85 (m, 3H), 1.76 - 1.44 (m, 6H), 1.20 (q, J = 10.2, 9.3 Hz, 2H).	430.35
1-(3-(4-氨基-7-甲基-5-(4-((四氢-2H-哌喃-4-基)氨基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.0 Hz, 1H), 7.35 (q, J = 7.3, 6.7 Hz, 4H), 6.51 (dd, J = 16.8, 10.3 Hz, 1H), 6.38 (dd, J = 16.8, 10.3 Hz, 1H), 6.08 (ddd, J = 16.8, 10.2, 2.5 Hz, 1H), 5.71 (ddd, J = 18.2, 10.2, 2.5 Hz, 1H), 5.62 (ddd, J = 20.1, 10.2, 2.5 Hz, 1H), 4.01 - 3.93 (m, 2H), 3.93 - 3.84 (m, 1H), 3.79 (s, 2H), 3.77 (s, 2H), 3.76 - 3.59 (m, 1H), 3.58 - 3.44 (m, 2H), 3.43 (d, J = 2.8 Hz, 1H), 3.36 - 3.21 (m, 1H), 2.89 - 2.79 (m, 1H), 2.10 (s, 1H), 2.08 (s, 1H), 1.97 (p, J = 10.9, 10.3 Hz, 1H), 1.72 (dq, J = 16.5, 12.6 Hz, 4H).	447.35
1-(4-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲基)吡啶-2(1H)-酮		^{1}H NMR (400 MHz, DMSO-d6) 8.11 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 6.9, 2.0 Hz, 1H), 7.46 (ddt, J = 8.7, 6.6, 1.9 Hz, 1H), 7.36 (d, J = 5.3 Hz, 4H), 6.56 - 6.34 (m, 2H), 6.31 - 6.23 (m, 1H), 6.08 (ddd, J = 16.8, 11.7, 2.4 Hz, 1H), 5.62 (ddd, J = 19.2, 10.3, 2.5 Hz, 1H), 5.18 (d, J = 1.7 Hz, 2H), 3.92 - 3.75 (m, 4H), 3.75 - 3.40 (m, 4H), 3.30 - 3.18 (m, 2H), 2.27 - 1.87 (m, 2H).	455.30

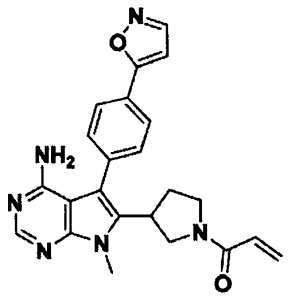
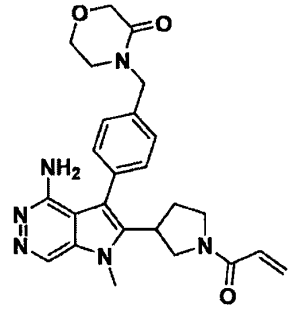
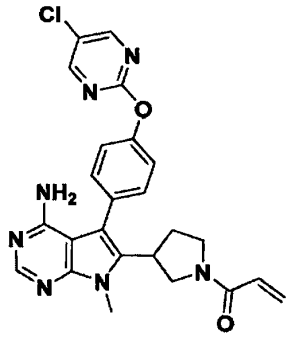
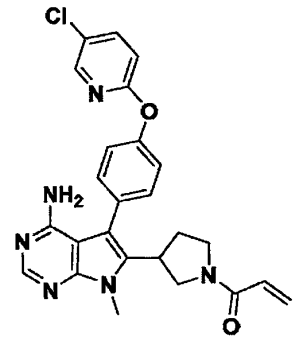
[1335]

化合物	结构	质子 NMR	MS [M+1]
1-[3-(4-氨基-5-{4-[环丙基(羟基)甲基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基]丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.12 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 7.7 Hz, 2H), 7.38 - 7.31 (m, 2H), 6.53- 6.43 (ddd, J = 16.9, 10.4, 3.3 Hz, 1H), 6.09 (ddd, J = 16.9, 8.8, 2.5 Hz, 1H), 5.76-5.63 (ddd, J = 16.5, 10.3, 2.4 Hz, 2H), 5.25 (dd, J = 4.5, 2.3 Hz, 1H), 4.06 (dd, J = 7.4, 4.4 Hz, 1H), 3.92 (t, J = 9.2 Hz, 1H), 3.79 (d, J = 6.5 Hz, 4H), 3.73-3.51 (dd, J = 21.7, 11.0 Hz, 3H), 3.31 - 3.21 (m, 1H), 2.20 -1.93 (m, 2H), 1.13-1.06 (m, 1H), 0.44 (td, J = 12.9, 6.6 Hz, 4H).	418.30
1-[3-(4-氨基-7-甲基-5-{4-[(3-甲基-1H-吡唑-1-基)甲基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基]丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.11 (t, J = 2.1 Hz, 1H), 7.73 (t, J = 2.6 Hz, 1H), 7.41-7.32 (m, 2H), 7.25 (dd, J = 8.3, 3.4 Hz, 1H), 7.14 (dd, J = 8.1, 3.7 Hz, 1H), 6.57-6.32 (m, 1H), 6.15-6.07 (m, 1H), 6.11-6.03 (m, 1H), 5.62 (ddt, J = 15.8, 10.3, 2.6 Hz, 1H), 5.38 (s, 1H), 5.32 (d, J = 2.7 Hz, 1H), 3.81-3.75 (m, 3H), 3.79-3.56 (m, 2H), 3.58-3.41 (m, 2H), 3.32-3.15 (m, 1H), 2.20 (dd, J = 21.3, 2.3 Hz, 3H), 2.10-1.89 (m, 2H).	442.25
1-(3-(4-氨基-7-甲基-5-(4-(4-甲基-1H-吡唑-1-基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.12 (d, J = 1.7 Hz, 1H), 7.87 (d, J = 8.1 Hz, 2H), 7.60 (s, 1H), 7.47 (d, J = 8.2 Hz, 2H), 6.47 (ddd, J = 31.9, 16.7, 10.2 Hz, 1H), 6.06 (ddd, J = 16.8, 7.5, 2.5 Hz, 1H), 5.60 (ddd, J = 21.7, 10.2, 2.5 Hz, 2H), 3.94 (d, J = 9.1 Hz, 1H), 3.79 (d, J = 6.3 Hz, 3H), 3.67 (q, J = 9.1 Hz, 1H), 3.60 - 3.45 (m, 1H), 3.29 (d, J = 10.7 Hz, 1H), 2.33 (d, J = 2.2 Hz, 1H), 2.13 (s, 5H).	428.25

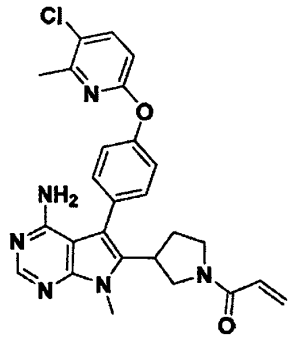
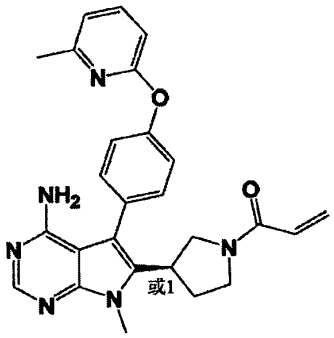
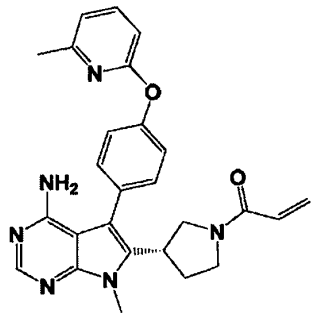
[1336]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-((5-(三氟甲基)吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) 8.68 - 8.58 (m, 1H), 8.27 (dt, J = 8.7, 2.8 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.32 (dd, J = 9.1, 4.1 Hz, 3H), 6.51 (ddd, J = 32.6, 16.8, 10.3 Hz, 1H), 6.13 (t, J = 1.9 Hz, 1H), 6.09 - 5.57 (m, 2H), 4.00 - 3.76 (m, 4H), 3.75 - 3.34 (m, 3H), 3.31 (s, 1H), 2.40 - 1.94 (m, 2H).	509.20
1-(3-(4-氨基-5-(4-(环戊烷羰基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 1.8 Hz, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 7.9 Hz, 2H), 6.55 - 6.35 (dd, J = 16.7, 10.3 Hz, 1H), 6.07 (ddd, J = 16.8, 7.0, 2.4 Hz, 1H), 5.63 - 5.58 (dd, J = 10.2, 2.5 Hz, 1H), 3.96 - 3.87 (m, 1H), 3.80 (d, J = 6.6 Hz, 4H), 3.77 (s, 1H), 3.68 (d, J = 8.9 Hz, 1H), 3.48 (t, J = 9.8 Hz, 1H), 3.27 (s, 1H), 2.21 (d, J = 7.3 Hz, 1H), 2.11 (s, 1H), 1.95 (s, 1H), 1.92 (d, J = 8.1 Hz, 1H), 1.80 (s, 2H), 1.64 (td, J = 8.4, 7.0, 4.9 Hz, 4H).	444.20
1-(5-(6-(1-丙烯酰基吡咯烷-3-基)-4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-基)吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (t, J = 6.8 Hz, 2H), 8.13 (d, J = 1.7 Hz, 1H), 7.86 - 7.78 (m, 1H), 6.47 (ddd, J = 32.7, 16.8, 10.3 Hz, 1H), 6.13 - 6.04 (m, 1H), 5.68 - 5.57 (m, 3H), 4.05 - 3.95 (t, J = 9.2 Hz, 3H), 3.79 (d, J = 6.8 Hz,3 H), 3.76 - 3.60 (m, 2H), 3.52 (dt, J = 16.6, 9.1 Hz, 2H), 3.27 (s, 1H), 2.61 (t, J = 8.0 Hz, 2H), 2.13 - 1.90 (m, 4H).	432.35

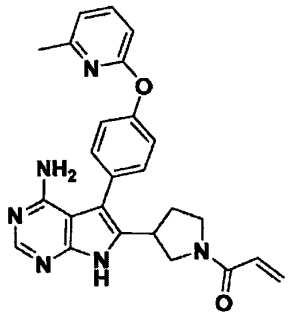
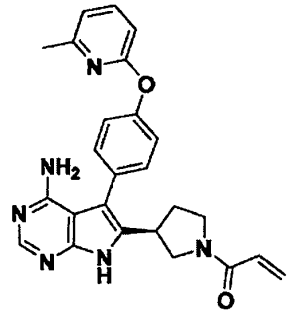
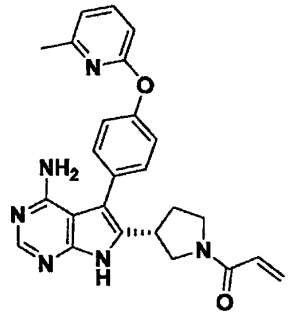
[1337]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-(异恶唑-5-基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 1.9 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 2.0 Hz, 1H), 6.51 - 6.42 (dd, J = 16.8, 10.2 Hz, 1H), 6.11 - 6.01 (m, 1H), 5.63 - 5.53 (m, 1H), 3.95 (t, J = 9.1 Hz, 1H), 3.80 (d, J = 6.7 Hz, 4H), 3.69 (s, 1H), 3.57 (t, J = 9.6 Hz, 1H), 3.53 (s, 1H), 3.52 - 3.43 (m, 1H), 3.28 (d, J = 9.7 Hz, 1H), 2.21 -1.97 (m, 2H).	415.15
4-[(4-{4-氨基-7-甲基-6-[1-(丙-2-烯酰基)吡咯烷-3-基]-7H-吡咯并[2,3-d]嘧啶-5-基}苯基)甲基]吗啉-3-酮		1H NMR (400 MHz, DMSO-d6) 8.12 (d, J = 2.2 Hz, 1H), 7.36 (qd, J = 8.2, 3.7 Hz, 4H), 6.51-6.39 (dd, J = 16.8, 10.3 Hz, 1H), 6.08 (dt, J = 16.8, 2.9 Hz, 1H), 5.84-5.47 (s, 2H), 4.63 (s, 2H), 4.15 (s, 2H), 3.94-3.83 (m, 2H), 3.84 -3.62 (m, 5H), 3.54 (dt, J = 8.0, 5.6 Hz, 2H), 3.52-3.21 (m, 3H), 2.21-1.91 (m, 3H).	461.30
1-(3-(4-氨基-5-(4-((5-氯嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 3.5 Hz, 2H), 8.13 (d, J = 1.7 Hz, 1H), 7.50 - 7.44 (m, 2H), 7.35 (d, J = 8.6 Hz, 2H), 6.51 (ddd, J = 33.8, 16.7, 10.3 Hz, 2H), 6.11 (ddd, J = 16.8, 5.5, 2.4 Hz, 1H), 5.74 - 5.44 (m, 3H), 4.01 - 3.91 (m, 1H), 3.80 (d, J = 6.8 Hz, 3H), 3.74 - 3.52 (m, 3H), 3.35 (d, J = 11.1 Hz, 1H), 2.20 - 2.04 (m, 2H).	476.20
1-(3-(4-氨基-5-(4-((5-氯吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.28 (dd, J = 7.5, 2.7 Hz, 1H), 8.13 (d, J = 2.2 Hz, 1H), 8.00 (dt, J = 8.8, 2.5 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.25 (dd, J = 8.6, 3.1 Hz, 2H), 7.22 - 7.15 (m, 1H), 6.50 (ddd, J = 33.1, 16.8, 10.3 Hz, 1H), 6.11 (dt, J = 16.8, 2.3 Hz, 1H), 5.64 (td, J = 10.2, 2.5 Hz, 1H), 3.95 (t, J = 9.2 Hz, 1H), 3.84 - 3.68 (m, 5H), 3.62 - 3.47 (m, 2H), 2.28 - 1.91 (m, 2H).	475.1

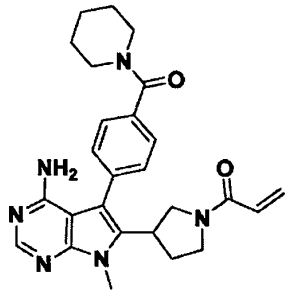
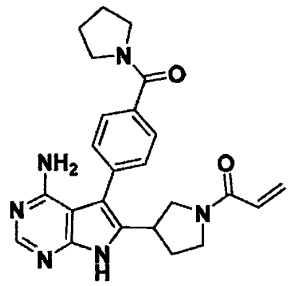
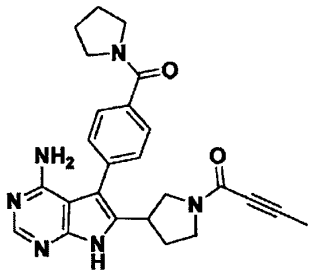
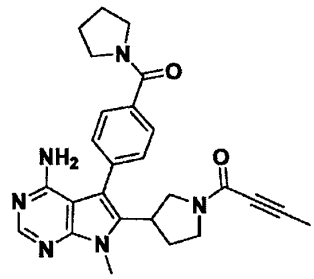
[1338]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-((5-氯-6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, 氯仿-d) δ 8.32 (d, J = 2.5 Hz, 1H), 7.68 (dd, J = 8.6, 1.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 2H), 7.23 (t, J = 7.2 Hz, 2H), 6.80 (t, J = 8.6 Hz, 1H), 6.48 - 6.22 (m, 2H), 5.69 (ddd, J = 15.2, 9.2, 3.0 Hz, 1H), 4.87 (s, 1H), 4.02 (dd, J = 11.4, 7.2 Hz, 0H), 3.92 - 3.80 (m, 3H), 3.80 - 3.47 (m, 2H), 2.53 (d, J = 4.4 Hz, 3H), 2.25 (q, J = 7.2 Hz, 1H), 2.03 (s, 1H).	490.2
(R)-1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 1.1 Hz, 1H), 7.79 - 7.72 (m, 1H), 7.45 - 7.39 (m, 2H), 7.20 (dd, J = 8.5, 3.7 Hz, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.84 (dd, J = 8.1, 4.2 Hz, 1H), 6.49 (ddd, J = 33.6, 16.8, 10.3 Hz, 1H), 6.10 (dt, J = 16.6, 2.0 Hz, 1H), 5.69 - 5.51 (m, 2H), 3.95 (t, J = 9.2 Hz, 1H), 3.80 (d, J = 6.5 Hz, 4H), 3.70 - 3.47 (m, 3H), 2.36 (d, J = 3.8 Hz, 3H), 2.27 - 1.93 (m, 2H).	455.20
(S)-1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 2.0 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.46 - 7.36 (m, 2H), 7.19 (dd, J = 8.6, 3.9 Hz, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.84 (dd, J = 8.1, 4.1 Hz, 1H), 6.49 (ddd, J = 33.2, 16.7, 10.2 Hz, 1H), 6.10 (dd, J = 16.7, 2.3 Hz, 1H), 5.63 (ddd, J = 10.8, 9.0, 2.4 Hz, 1H), 3.95 (t, J = 9.0 Hz, 1H), 3.79 (d, J = 6.8 Hz, 4H), 3.53 (dq, J = 18.8, 9.7 Hz, 2H), 2.36 (d, J = 3.8 Hz, 3H), 2.27 - 1.94 (m, 2H).	455.20

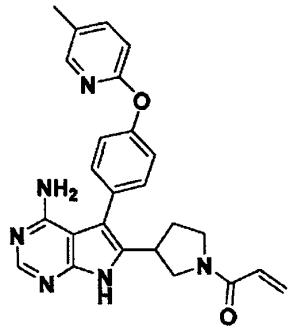
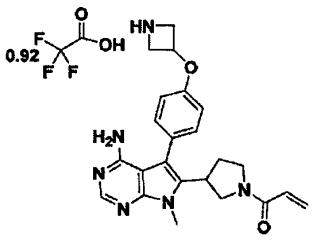
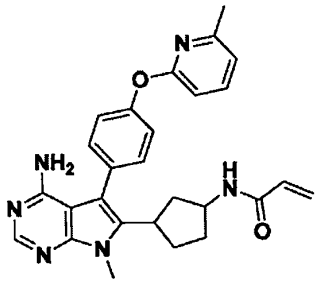
[1339]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (d, J = 2.6 Hz, 1H), 8.09 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.22 (dd, J = 8.5, 2.1 Hz, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.58 (ddd, J = 16.7, 10.3, 3.8 Hz, 1H), 6.15 (dd, J = 16.7, 2.5 Hz, 1H), 5.67 (ddd, J = 10.6, 8.5, 2.5 Hz, 2H), 3.99 (t, J = 8.8 Hz, 1H), 3.89 - 3.77 (m, 1H), 3.77 - 3.60 (m, 1H), 3.54 (dt, J = 11.0, 5.4 Hz, 1H), 3.42 (d, J = 6.8 Hz, 1H), 2.37 (s, 3H), 2.36 - 2.07 (m, 2H).	441.30
(S)-1-(3-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 8.09 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.43 (dd, J = 8.5, 3.5 Hz, 2H), 7.27 - 7.19 (m, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.59 (ddd, J = 16.8, 10.3, 3.9 Hz, 1H), 6.15 (dd, J = 16.8, 2.5 Hz, 1H), 5.76 (s, 1H), 5.67 (ddd, J = 10.7, 8.5, 2.5 Hz, 1H), 4.06 - 3.78 (m, 1H), 3.77 - 3.60 (m, 1H), 3.54 (dt, J = 11.2, 5.4 Hz, 1H), 3.42 (d, J = 6.9 Hz, 1H), 2.37 (s, 3H), 2.37 - 2.10 (m, 2H).	441.30
(R)-1-(3-(4-氨基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 - 11.73 (m, 1H), 8.09 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.43 (dd, J = 8.4, 3.5 Hz, 2H), 7.27 - 7.16 (m, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.58 (ddd, J = 16.8, 10.3, 3.8 Hz, 1H), 6.15 (dd, J = 16.7, 2.5 Hz, 1H), 5.90 - 5.75 (m, 2H), 5.67 (ddd, J = 10.6, 8.5, 2.5 Hz, 1H), 4.08 - 3.78 (m, 1H), 3.68 (dt, J = 28.8, 11.1 Hz, 1H), 3.55 (td, J = 10.7, 6.7 Hz, 1H), 3.50 - 3.39 (m, 1H), 2.37 (s, 3H), 2.30 (q, J = 8.9, 7.8 Hz, 0H), 2.23 - 2.08 (m, 1H).	441.25

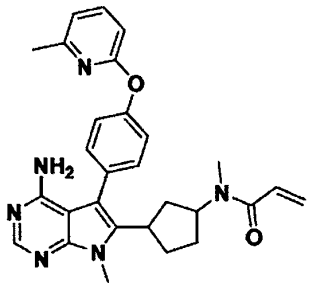
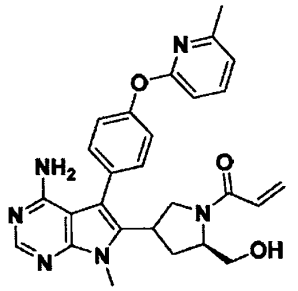
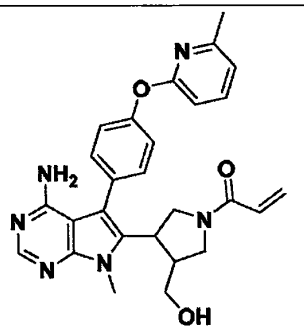
[1340]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-(哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.13 (d, J = 2.8 Hz, 1H), 7.45 (d, J = 6.8 Hz, 4H), 6.46 (ddd, J = 40.4, 16.8, 10.4 Hz, 1H), 6.08 (dt, J = 16.8, 2.4 Hz, 1H), 5.62 (ddd, J = 12.9, 10.4, 2.4 Hz, 1H), 3.96 - 3.87 (m, 0H), 3.79 (d, J = 7.6 Hz, 3H), 3.69 (q, J = 8.2 Hz, 1H), 3.61 - 3.44 (m, 1H), 2.23 (s, 1H), 2.03 (ddt, J = 50.6, 20.8, 10.4 Hz, 2H), 1.67 - 1.61 (m, 2H), 1.54 (s, 5H).	459.3
1-(3-(4-氨基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.10 (d, J = 1.0 Hz, 1H), 7.72 - 7.60 (m, 2H), 7.45 (dd, J = 8.1, 3.6 Hz, 2H), 6.58 (ddd, J = 16.7, 10.3, 4.3 Hz, 1H), 6.14 (dd, J = 16.7, 2.5 Hz, 1H), 5.67 (ddd, J = 10.8, 8.8, 2.5 Hz, 3H), 3.83 (q, J = 9.2 Hz, 1H), 3.76 - 3.59 (m, 1H), 3.59 - 3.38 (m, 6H), 2.39 - 2.05 (m, 2H), 1.86 (dq, J = 19.0, 6.8 Hz, 4H).	431.15
1-(3-(4-氨基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丁-2-炔-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 - 11.71 (m, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.64 (dd, J = 7.9, 4.8 Hz, 2H), 7.44 (dd, J = 7.9, 5.7 Hz, 2H), 5.68 (d, J = 65.3 Hz, 2H), 3.98 - 3.80 (m, 1H), 3.77 - 3.58 (m, 2H), 3.50 (t, J = 6.7 Hz, 4H), 3.38 (d, J = 11.0 Hz, 1H), 3.28 - 3.20 (m, 1H), 2.35 - 2.11 (m, 2H), 2.02 (s, 1H), 1.98 (s, 2H), 1.87 (dq, J = 19.0, 6.7 Hz, 4H).	443.25
1-(3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丁-2-炔-1-酮		^{1}H NMR (400 MHz, 氯仿-d) δ 8.32 (d, J = 3.3 Hz, 1H), 7.68 (t, J = 9.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.86 (s, 2H), 3.99 - 3.82 (m, 5H), 3.69 (dt, J = 21.4, 8.0 Hz, 5H), 3.65 - 3.47 (m, 4H), 2.24 - 2.10 (m, 2H), 2.07 - 1.93 (m, 6H), 1.86 (s, 6H).	457.35

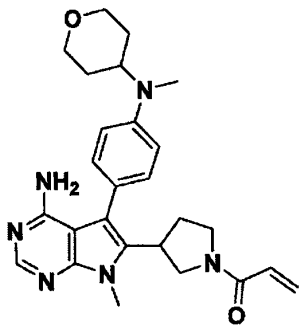
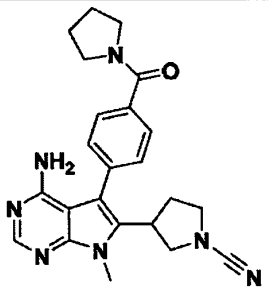
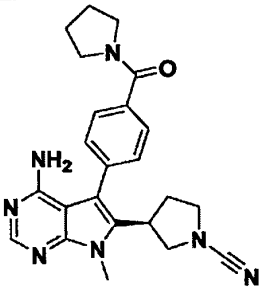
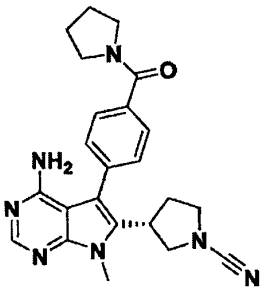
[1341]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-5-(4-((5-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (d, J = 2.5 Hz, 1H), 8.07 (dd, J = 19.5, 1.7 Hz, 2H), 7.71 (dd, J = 8.3, 2.5 Hz, 1H), 7.41 (dd, J = 8.5, 3.7 Hz, 2H), 7.24 - 7.16 (m, 2H), 7.02 (d, J = 8.3 Hz, 1H), 6.58 (ddd, J = 16.8, 10.3, 2.8 Hz, 1H), 6.15 (dd, J = 16.8, 2.5 Hz, 1H), 5.75 (s, 1H), 5.67 (ddd, J = 10.8, 8.7, 2.5 Hz, 2H), 3.99 (dd, J = 9.9, 7.9 Hz, 1H), 3.87 - 3.77 (m, 1H), 3.75 - 3.59 (m, 1H), 3.54 (tt, J = 12.8, 6.9 Hz, 1H), 3.41 (dd, J = 9.5, 6.1 Hz, 1H), 2.27 (s, 4H), 2.22 - 2.05 (m, 2H).	441.15
1-(3-{4-氨基-5-[4-(氮杂环丁-3-基氧基)苯基]-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡咯烷-1-基)丙-2-烯-1-酮;三氟乙酸盐		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (d, J = 52.2 Hz, 2H), 8.58 - 8.34 (m, 1H), 7.35 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.44 (ddd, J = 53.6, 16.7, 10.3 Hz, 1H), 6.09 (ddd, J = 16.8, 4.6, 2.4 Hz, 1H), 5.64 (ddd, J = 13.9, 10.3, 2.4 Hz, 1H), 5.15 (t, J = 6.1 Hz, 1H), 4.50 (s, 2H), 4.07 (d, J = 10.2 Hz, 2H), 3.97 - 3.43 (m, 7H), 3.28 (dt, J = 12.0, 9.1 Hz, 1H), 2.31 - 1.85 (m, 2H).	419.30
N-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环戊基)丙烯酰胺		1H NMR (400 MHz, DMSO-d6) δ 8.15 (d, J = 12.7 Hz, 2H), 7.77 (td, J = 7.7, 1.6 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.26 - 7.19 (m, 2H), 7.05 (d, J = 7.3 Hz, 1H), 6.85 (dd, J = 8.2, 4.6 Hz, 1H), 6.24 - 6.15 (m, 1H), 6.06 (dd, J = 17.1, 2.4 Hz, 1H), 5.56 (ddd, J = 10.0, 3.7, 2.4 Hz, 1H), 4.27 - 4.03 (m, 1H), 3.81 (d, J = 10.3 Hz, 3H), 3.65 (d, J = 43.2 Hz, 1H), 2.37 (s, 3H), 2.18 (s, 1H), 2.12 - 1.77 (m, 3H), 1.68 (q, J = 12.0 Hz, 1H), 1.62 - 1.48 (m, 1H).	469

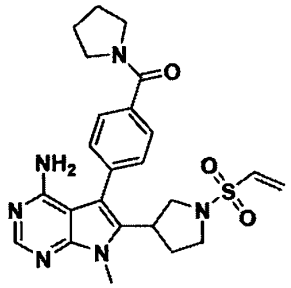
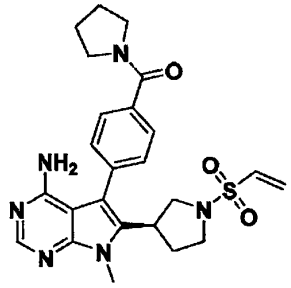
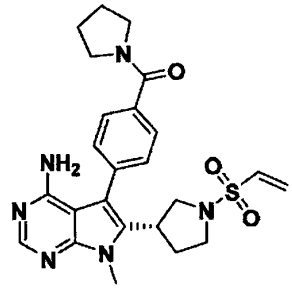
[1342]

化合物	结构	质子 NMR	MS [M+1]
N-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环戊基)-N-甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.06 (t, J = 15.7 Hz, 1H), 5.63 (s, 2H), 4.69 (d, J = 173.3 Hz, 1H), 3.78 (s, 3H), 3.43 (d, J = 10.4 Hz, 1H), 2.67 (d, J = 54.3 Hz, 3H), 2.35 (s, 3H), 2.11 - 1.50 (m, 6H).	483.20
1-((2R)-4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-(羟基甲基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.13 (s, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.42 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 7.2 Hz, 1H), 6.88 - 6.80 (m, 1H), 6.53 (dd, J = 16.4, 10.4 Hz, 1H), 6.11 (d, J = 17.0 Hz, 1H), 5.64 (dd, J = 10.4, 2.4 Hz, 1H), 4.07 (s, 1H), 3.98 (s, 1H), 3.82 (d, J = 7.4 Hz, 3H), 3.58 - 3.46 (m, 2H), 2.35 (s, 3H).	485.22
1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-(羟基甲基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 1.2 Hz, 1H), 7.75 (td, J = 7.8, 3.3 Hz, 1H), 7.49 - 7.28 (m, 2H), 7.16 (ddd, J = 19.5, 8.4, 3.9 Hz, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.82 (dd, J = 8.1, 1.9 Hz, 1H), 6.42 (dd, J = 16.7, 10.3 Hz, 1H), 6.20 (dd, J = 16.8, 10.1 Hz, 1H), 6.04 - 5.58 (ddd, J = 10.2, 3.9, 2.5 Hz, 2H), 4.62 (dt, J = 15.6, 5.0 Hz, 1H), 3.95 (dq, J = 37.7, 8.1 Hz, 1H), 3.79 (s, 3H), 3.62 (ddd, J = 17.2, 11.4, 7.4 Hz, 1H), 3.52 - 3.35 (m, 1H), 3.18 (dq, J = 10.2, 5.1 Hz, 1H), 3.12 - 3.00 (m, 1H), 2.84 - 2.65 (m, 1H), 2.36 (d, J = 7.9 Hz, 3H), 2.08 (s, 2H).	485.40

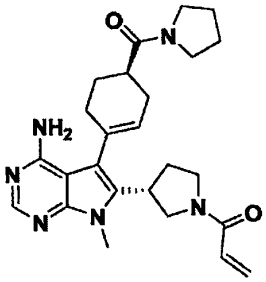
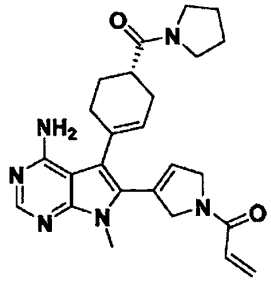
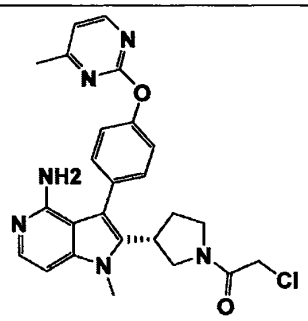
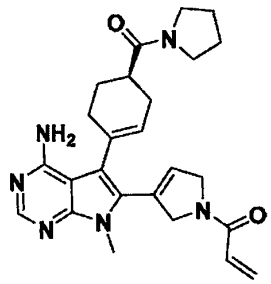
[1343]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-(甲基(四氢-2H-哌喃-4-基)氨基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.0 Hz, 1H), 7.35 (q, J = 7.3, 6.7 Hz, 4H), 6.51 (dd, J = 16.8, 10.3 Hz, 1H), 6.38 (dd, J = 16.8, 10.3 Hz, 0H), 6.08 (ddd, J = 16.8, 10.2, 2.5 Hz, 1H), 5.71 (ddd, J = 18.2, 10.2, 2.5 Hz, 1H), 5.62 (ddd, J = 20.1, 10.2, 2.5 Hz, 1H), 4.01 - 3.93 (m, 2H), 3.93 - 3.84 (m, 1H), 3.79 (s, 2H), 3.77 (s, 2H), 3.76 - 3.59 (m, 1H), 3.58 - 3.44 (m, 2H), 3.43 (d, J = 2.8 Hz, 1H), 3.36 - 3.21 (m, 1H), 2.89 - 2.79 (m, 1H), 2.78 (d, J = 7.0 Hz, 3H), 2.10 (s, 1H), 2.08 (s, 1H), 1.97 (p, J = 10.9, 10.3 Hz, 1H), 1.72 (dq, J = 16.5, 12.6 Hz, 4H).	461.35
3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.67 - 7.60 (m, 2H), 7.48 - 7.41 (m, 2H), 5.59 (s, 2H), 3.79 (s, 3H), 3.73 (td, J = 9.2, 8.7, 6.9 Hz, 1H), 3.66 (t, J = 8.8 Hz, 1H), 3.55 - 3.42 (m, 5H), 3.46 - 3.33 (m, 2H), 2.15 (ddd, J = 14.4, 7.3, 4.8 Hz, 1H), 2.06 - 1.80 (m, 5H).	416.20
(S)-3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.67 - 7.60 (m, 2H), 7.48 - 7.41 (m, 2H), 5.59 (s, 2H), 3.79 (s, 3H), 3.73 (td, J = 9.2, 8.7, 6.9 Hz, 1H), 3.66 (t, J = 8.8 Hz, 1H), 3.55 - 3.42 (m, 5H), 3.46 - 3.33 (m, 2H), 2.15 (ddd, J = 14.4, 7.3, 4.8 Hz, 1H), 2.06 - 1.80 (m, 5H).	416.20
(R)-3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.67 - 7.60 (m, 2H), 7.48 - 7.41 (m, 2H), 5.59 (s, 2H), 3.79 (s, 3H), 3.73 (td, J = 9.2, 8.7, 6.9 Hz, 1H), 3.66 (t, J = 8.8 Hz, 1H), 3.55 - 3.42 (m, 5H), 3.46 - 3.33 (m, 2H), 2.15 (ddd, J = 14.4, 7.3, 4.8 Hz, 1H), 2.06 - 1.80 (m, 5H).	416.20

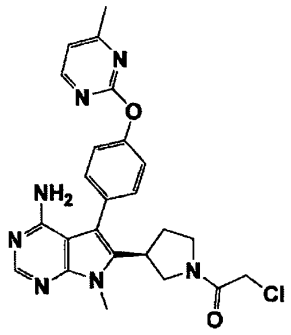
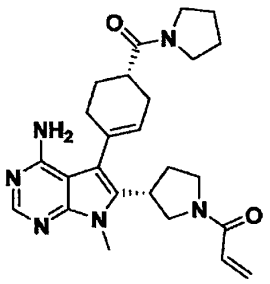
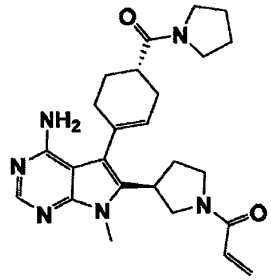
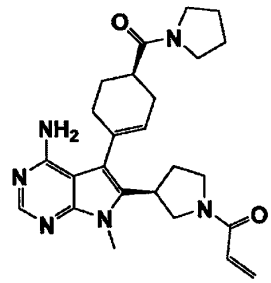
[1344]

化合物	结构	质子 NMR	MS [M+1]
(4-(4-氨基-7-甲基-6-(1-(乙烯基磺酰基)吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.66 - 7.59 (m, 2H), 7.46 - 7.40 (m, 2H), 6.74 (dd, J = 16.5, 10.0 Hz, 1H), 6.12 (d, J = 10.0 Hz, 1H), 6.04 (d, J = 16.5 Hz, 1H), 5.58 (s, 1H), 3.78 (s, 3H), 3.67 (q, J = 9.4, 8.9 Hz, 1H), 3.49 (ddd, J = 13.2, 8.5, 6.2 Hz, 5H), 3.32 - 3.25 (m, 1H), 3.18 (td, J = 10.0, 6.6 Hz, 1H), 3.10 (t, J = 10.1 Hz, 1H), 2.17 (dq, J = 12.8, 7.0, 6.2 Hz, 1H), 2.01 - 1.81 (m, 5H).	481.20
(R)-(4-(4-氨基-7-甲基-6-(1-(乙烯基磺酰基)吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.66 - 7.59 (m, 2H), 7.46 - 7.40 (m, 2H), 6.74 (dd, J = 16.5, 10.0 Hz, 1H), 6.12 (d, J = 10.0 Hz, 1H), 6.04 (d, J = 16.5 Hz, 1H), 5.58 (s, 1H), 3.78 (s, 3H), 3.67 (q, J = 9.4, 8.9 Hz, 1H), 3.49 (ddd, J = 13.2, 8.5, 6.2 Hz, 5H), 3.32 - 3.25 (m, 1H), 3.18 (td, J = 10.0, 6.6 Hz, 1H), 3.10 (t, J = 10.1 Hz, 1H), 2.17 (dq, J = 12.8, 7.0, 6.2 Hz, 1H), 2.01 - 1.81 (m, 5H).	481.20
(S)-(4-(4-氨基-7-甲基-6-(1-(乙烯基磺酰基)吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.66 - 7.59 (m, 2H), 7.46 - 7.40 (m, 2H), 6.74 (dd, J = 16.5, 10.1 Hz, 1H), 6.12 (d, J = 10.0 Hz, 1H), 6.04 (d, J = 16.6 Hz, 1H), 5.60 (s, 1H), 3.78 (s, 3H), 3.67 (q, J = 9.9, 9.5 Hz, 1H), 3.49 (ddd, J = 13.2, 8.5, 6.3 Hz, 5H), 3.32 - 3.25 (m, 1H), 3.18 (td, J = 10.1, 6.7 Hz, 1H), 3.10 (t, J = 10.1 Hz, 1H), 2.17 (dt, J = 12.9, 7.1 Hz, 1H), 2.01 - 1.81 (m, 5H).	481.20

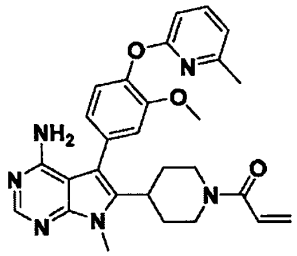
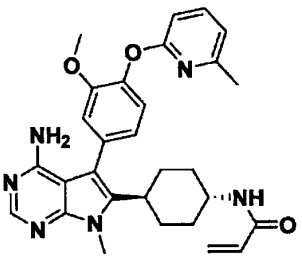
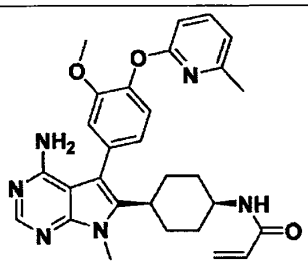
[1345]

化合物	结构	质子 NMR	MS [M+1]
1-((R)-3-(4-氨基-7-甲基-5-((R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.01 (s, 1H), 6.62 (dt, J = 16.7, 11.2 Hz, 1H), 6.46 (s, 1H), 6.17 (dt, J = 16.8, 2.5 Hz, 1H), 5.69 (td, J = 10.0, 2.6 Hz, 1H), 4.05 - 3.80 (m, 2H), 3.68 (d, J = 5.9 Hz, 5H), 3.61 - 3.44 (m, 3H), 3.43 - 3.36 (m, 1H), 3.30 (d, J = 6.9 Hz, 2H), 2.91 (s, 1H), 2.23 (q, J = 36.2, 32.0 Hz, 6H), 1.90 (p, J = 6.7 Hz, 3H), 1.79 (p, J = 6.8 Hz, 3H).	449.25
(S)-1-(3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 6.62 (dt, J = 17.4, 9.1 Hz, 3H), 6.21 (d, J = 16.1 Hz, 2H), 5.75 (d, J = 9.3 Hz, 2H), 4.53 (dd, J = 88.7, 39.5 Hz, 4H), 3.73 (s, 3H), 3.63 - 3.47 (m, 2H), 3.31 (s, 2H), 2.96 (d, J = 9.2 Hz, 1H), 2.30 (s, 2H), 2.17 (d, J = 7.2 Hz, 2H), 1.85 (dq, J = 36.4, 6.8 Hz, 6H).	447.25
(R)-1-(3-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)-2-氯乙-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (dd, J = 4.9, 3.1 Hz, 1H), 8.13 (d, J = 2.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 5.0 Hz, 1H), 4.37 - 4.08 (m, 2H), 3.93 - 3.41 (m, 7H), 3.25 (s, 1H), 2.43 (s, 3H), 2.36 - 1.92 (m, 2H).	478.25
(R)-1-(3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 6.62 (dt, J = 17.4, 9.1 Hz, 3H), 6.21 (d, J = 16.1 Hz, 2H), 5.75 (d, J = 9.3 Hz, 2H), 4.53 (dd, J = 88.7, 39.5 Hz, 4H), 3.73 (s, 3H), 3.63 - 3.47 (m, 2H), 3.31 (s, 2H), 2.96 (d, J = 9.2 Hz, 1H), 2.30 (s, 2H), 2.17 (d, J = 7.2 Hz, 2H), 1.85 (dq, J = 36.4, 6.8 Hz, 6H).	447.25

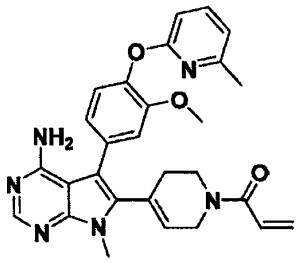
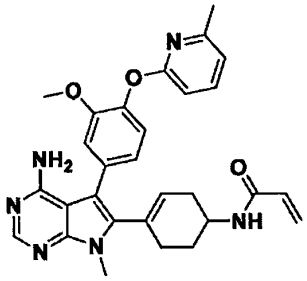
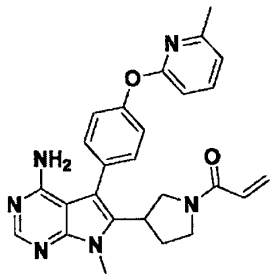
[1346]

化合物	结构	质子 NMR	MS [M+1]
(S)-1-(3-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)-2-氯乙-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (dd, J = 5.0, 3.0 Hz, 1H), 8.13 (d, J = 2.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 5.0 Hz, 1H), 5.60 (s, 1H), 4.37 - 4.09 (m, 2H), 3.66 (dd, J = 105.6, 8.9 Hz, 7H), 3.28 (d, J = 23.2 Hz, 1H), 2.43 (s, 3H), 2.31 - 1.96 (m, 2H).	478.25
1-((R)-3-(4-氨基-7-甲基-5-((S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		1H NMR (400 MHz, DMSO-d6) δ 8.01 (s, 1H), 6.62 (dt, J = 16.7, 11.2 Hz, 1H), 6.46 (s, 1H), 6.17 (dt, J = 16.8, 2.5 Hz, 1H), 5.69 (td, J = 10.0, 2.6 Hz, 1H), 4.05 - 3.80 (m, 2H), 3.68 (d, J = 5.9 Hz, 5H), 3.61 - 3.44 (m, 3H), 3.43 - 3.36 (m, 1H), 3.30 (d, J = 6.9 Hz, 2H), 2.91 (s, 1H), 2.23 (q, J = 36.2, 32.0 Hz, 6H), 1.90 (p, J = 6.7 Hz, 3H), 1.79 (p, J = 6.8 Hz, 3H).	449.25
1-((S)-3-(4-氨基-7-甲基-5-((S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 6.63 (dd, J = 16.7, 10.3 Hz, 1H), 6.43 (s, 1H), 6.24 - 6.05 (m, 1H), 5.69 (dt, J = 8.9, 2.9 Hz, 2H), 3.99 (s, 1H), 3.68 (d, J = 7.9 Hz, 6H), 3.61 - 3.45 (m, 2H), 3.41 (d, J = 9.5 Hz, 1H), 3.31 (d, J = 9.9 Hz, 2H), 2.90 (s, 1H), 2.44 - 2.31 (m, 1H), 2.24 (d, J = 19.4 Hz, 3H), 2.11 (d, J = 18.0 Hz, 2H), 1.89 (q, J = 6.7, 6.2 Hz, 3H), 1.79 (p, J = 6.7 Hz, 2H).	449.25
1-((S)-3-(4-氨基-7-甲基-5-((R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 6.62 (dt, J = 16.6, 11.1 Hz, 1H), 6.45 (s, 1H), 6.17 (dt, J = 16.8, 2.6 Hz, 1H), 5.69 (td, J = 11.1, 10.0, 3.6 Hz, 2H), 4.12 - 3.36 (m, 10H), 3.30 (s, 1H), 2.91 (s, 1H), 2.47 - 1.95 (m, 6H), 1.85 (dq, J = 36.9, 6.8 Hz, 6H).	449.30

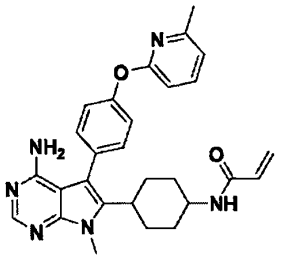
[1347]

化合物	结构	质子 NMR	MS [M+1]
1-[4-(4-氨基-5-{3-甲氧基-4-[(6-甲基吡啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)哌啶-1-基]丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.10 - 7.05 (m, 1H), 6.94 (d, J = 7.3 Hz, 2H), 6.76 (dd, J = 16.7, 10.5 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.04 (dd, J = 16.7, 2.4 Hz, 1H), 5.61 (dd, J = 10.4, 2.5 Hz, 2H), 4.47 (s, 1H), 4.13 - 4.06 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.09 (s, 2H), 2.64 (s, 2H), 2.31 (s, 3H), 1.83 (s, 2H), 1.57 (s, 2H).	498.587
N-((1r,4r)-4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)环己基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.11 (s, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 8.0, 1.9 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.22 (d, J = 6.0 Hz, 2H), 5.65 (t, J = 6.0 Hz, 1H), 4.60 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.70 (s, 1H), 2.98 (t, J = 12.5 Hz, 1H), 2.42 (s, 3H), 2.01 (d, J = 14.2 Hz, 2H), 1.94 (s, 2H), 1.81 (d, J = 12.7 Hz, 1H), 1.75 (d, J = 12.6 Hz, 1H), 1.45 - 1.29 (m, 2H).	512.614
N-((1s,4s)-4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)环己基)丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.11 (s, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 8.0, 1.9 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.22 (d, J = 6.0 Hz, 2H), 5.65 (t, J = 6.0 Hz, 1H), 4.60 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.70 (s, 1H), 2.98 (t, J = 12.5 Hz, 1H), 2.42 (s, 3H), 2.01 (d, J = 14.2 Hz, 2H), 1.94 (s, 2H), 1.81 (d, J = 12.7 Hz, 1H), 1.75 (d, J = 12.6 Hz, 1H), 1.45 - 1.29 (m, 2H).	512.614

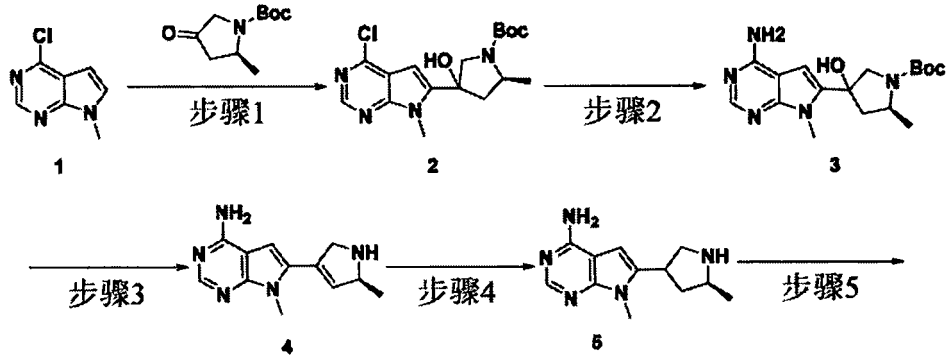
[1348]

化合物	结构	质子 NMR	MS [M+1]
1-[4-(4-氨基-5-{3-甲氧基-4-[(6-甲基吡啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1,2,3,6-四氢吡啶-1-基]丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 2.6 Hz, 1H), 6.95 (dd, J = 9.6, 7.6 Hz, 2H), 6.79 (ddd, J = 26.2, 16.7, 10.4 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.12 (dq, J = 16.7, 2.5 Hz, 1H), 6.05 (s, 2H), 5.73 - 5.64 (m, 1H), 4.25 (s, 1H), 4.16 (d, J = 3.3 Hz, 1H), 3.69 - 3.60 (m, 8H), 2.31 (s, 3H), 2.17 (d, J = 11.8 Hz, 2H).	496.571
N-(4-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)环己-3-烯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.72 - 7.64 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 7.01 - 6.91 (m, 2H), 6.68 (d, J = 8.2 Hz, 1H), 6.22 (dd, J = 17.1, 10.0 Hz, 1H), 6.09 (dd, J = 17.1, 2.4 Hz, 2H), 5.86 (dt, J = 4.9, 2.4 Hz, 1H), 5.58 (dd, J = 10.0, 2.4 Hz, 1H), 3.93 (q, J = 8.9 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.48 - 2.38 (m, 1H), 2.30 (s, 3H), 2.21 (d, J = 10.1 Hz, 1H), 2.13 - 2.01 (m, 2H), 1.87 - 1.79 (m, 1H), 1.52 (qd, J = 11.2, 5.2 Hz, 1H).	510.598
1-(3-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 2.1 Hz, 1H), 7.80 - 7.71 (m, 1H), 7.45 - 7.38 (m, 2H), 7.19 (dd, J = 8.6, 3.9 Hz, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.84 (dd, J = 8.2, 4.1 Hz, 1H), 6.49 (ddd, J = 33.0, 16.8, 10.3 Hz, 1H), 6.10 (dt, J = 16.8, 1.9 Hz, 1H), 5.63 (ddd, J = 10.8, 8.9, 2.5 Hz, 2H), 4.00 - 3.91 (m, 1H), 3.79 (d, J = 6.8 Hz, 4H), 3.68 (t, J = 9.3 Hz, 1H), 3.53 (dq, J = 18.9, 9.5 Hz, 2H), 2.36 (d, J = 3.8 Hz, 3H), 2.28 - 2.20 (m, 1H), 2.17 - 1.93 (m, 1H).	454.534

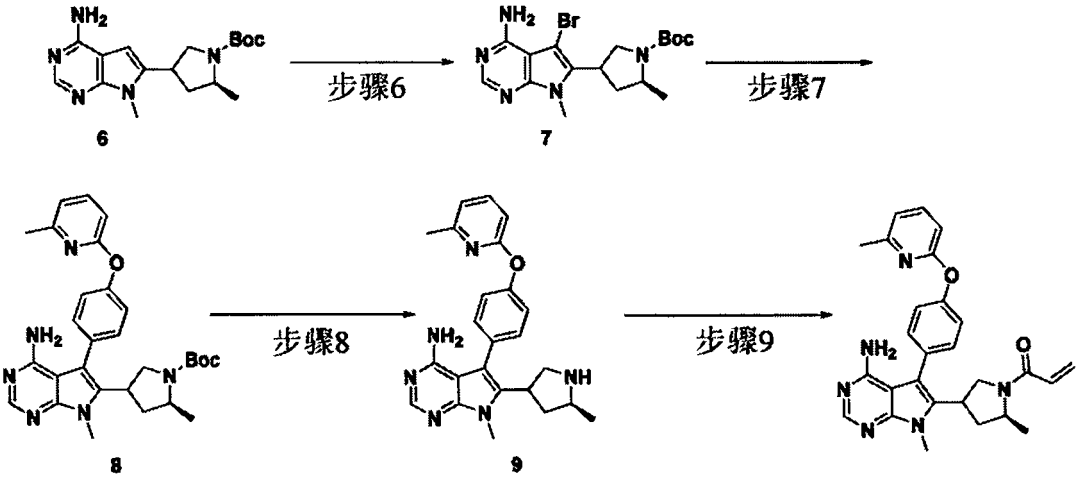
[1349]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环己基)丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.25 (s, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.47 - 7.39 (m, 2H), 7.30 - 7.23 (m, 2H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.21 (dd, *J* = 16.9, 1.4 Hz, 1H), 5.97 (dd, *J* = 16.9, 10.3 Hz, 1H), 5.80 - 5.72 (m, 1H), 5.56 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.36 (d, *J* = 7.2 Hz, 1H), 4.26 - 4.19 (m, 1H), 3.87 (s, 3H), 2.92 (dd, *J* = 16.9, 10.3 Hz, 1H), 2.44 (s, 3H), 1.94 (d, *J* = 11.5 Hz, 2H), 1.74 (d, *J* = 11.2 Hz, 2H).	482.588

[1350] 实例15

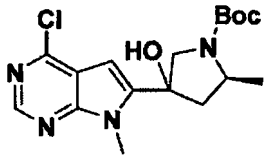


[1351]



[1352] (2S)-4-(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基-2-甲基吡咯烷-1-甲酸叔丁酯

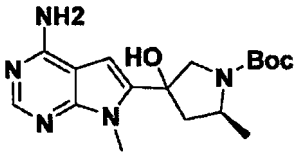
[1353]



[1354] 步骤1:向圆底烧瓶中装入4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶(1.7g,10.18mmol)、THF(30mL)及搅拌棒。在-78℃下,向上述溶液中逐滴添加LDA(7.63mL,

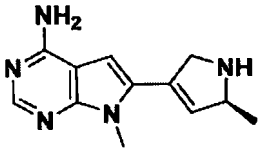
15.26mmol,2M),在相同温度下搅拌1小时之后,在-78℃下添加含有(S)-2-甲基-4-侧氧基吡咯烷-1-甲酸叔丁酯(4.05g,20.35mmol)的THF(10mL),且使混合物升温至室温维持1小时。混合物用饱和NH4Cl(10mL)淬灭,且用EtOAc(40mL)萃取3次,合并的有机相用盐水洗涤,经Na_2SO_4干燥且在减压下合并。所得粗产物通过硅胶色谱纯化(用PE/EtOAc=2:1洗脱),得到呈灰白色固体状的(2S)-4-(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基-2-甲基吡咯烷-1-甲酸叔丁酯(550mg,1.50mmol,15%)。

[1355] (2S)-4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基-2-甲基吡咯烷-1-甲酸叔丁酯

[1356] 

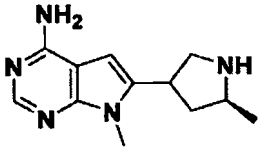
[1357] 步骤2:向50mL未密封试管中装入(2S)-4-(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基-2-甲基吡咯烷-1-甲酸叔丁酯(550mg,1.50mmol)、NH3/H2O(10mL,25%~30%)及1,4-二恶烷(10mL),密封所述试管,且在100℃下搅拌混合物溶液12小时。将试管冷却至室温且倒出混合物,浓缩溶剂,粗产物用DCM(100mL)洗涤3次,浓缩且得到呈灰白色固体状的(2S)-4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基-2-甲基吡咯烷-1-甲酸叔丁酯(400mg,77%)。

[1358] (S)-7-甲基-6-(5-甲基-2,5-二氢-1H-吡咯-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1359] 

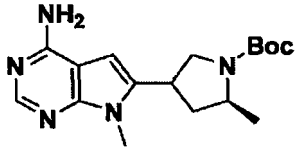
[1360] 步骤3:向圆底烧瓶中装入(2S)-4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基-2-甲基吡咯烷-1-甲酸叔丁酯(380mg,1.09mmol)、HCl(5mL)及搅拌棒。在100℃下搅拌混合物2小时。冷却至室温后,将所得混合物浓缩且用水(10mL)稀释,将pH调节至7-8,且用DCM(20mL)萃取3次。合并有机相且在减压下浓缩,得到呈棕色固体状的粗产物(S)-7-甲基-6-(5-甲基-2,5-二氢-1H-吡咯-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(330mg)。

[1361] 7-甲基-6-((5S)-5-甲基吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1362] 

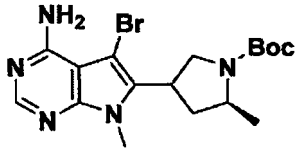
[1363] 步骤4:向可再密封的反应瓶中装入(S)-7-甲基-6-(5-甲基-2,5-二氢-1H-吡咯-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(330mg,粗物质)、Pd/C(30mg)及MeOH(10mL)及搅拌棒。将混合物抽真空且用氮气吹扫三次,然后抽真空且用氢气吹扫五次。在50℃下搅拌混合物整夜。随后过滤混合物,用MeOH洗涤滤饼5次,浓缩有机相,得到呈棕色固体状的7-甲基-6-((5S)-5-甲基吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(220mg,63%(两个步骤))。

[1364] (2S)-4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-甲酸叔丁酯

[1365] 

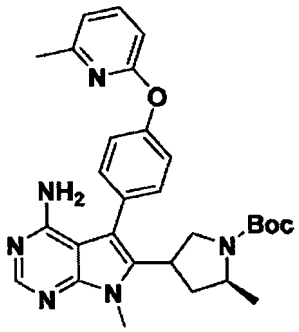
[1366] 步骤5:向圆底烧瓶中装入7-甲基-6-((5S)-5-甲基吡咯烷-3-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(220mg,0.95mmol)、TEA(288mg,2.85mmol)、MeOH(5mL)及搅拌棒。添加Boc2O(308mg,1.42mmol),且在室温下搅拌溶液12小时。混合物用水(10mL)稀释,用DCM(50mL)萃取3次。合并有机相且用盐水洗涤,经Na_2SO_4干燥,真空浓缩,通过使用DCM/MeOH(20:1)制备型TLC纯化粗产物,得到呈棕色固体状的(2S)-4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-甲酸叔丁酯(190mg,60%)。

[1367] (2S)-4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-甲酸叔丁酯

[1368] 

[1369] 步骤6:向圆底烧瓶中装入(2S)-4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2-甲基吡咯烷-1-甲酸叔丁酯(180mg,543μmol)、二甲基甲酰胺(15mL)及搅拌棒。添加NBS(101mg,570μmolμmol),且在0℃下搅拌溶液1小时。混合物用DCM(50mL)稀释,用水及盐水洗涤,经无水Na_2SO_4干燥,在减压下浓缩,通过使用DCM:MeOH(12:1)的制备型TLC纯化粗产物,得到呈棕色固体状的(2S)-4-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2-甲基吡咯烷-1-甲酸叔丁酯(200mg,85%)。

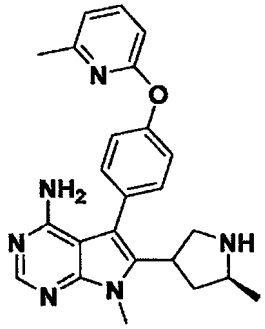
[1370] (2S)-4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-甲酸叔丁酯

[1371] 

[1372] 步骤7:向可再密封的反应瓶中装入(2S)-4-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2-甲基吡咯烷-1-甲酸叔丁酯(200mg,487μmol)、2-甲基-6-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]吡啶(181mg,584μmol)、K3PO4(309mg,1.46mmol)、Pd(DtBPF)C12(47.5mg,73.0μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF:水=16:1(10mL),且在90℃下搅拌溶液1小时。混合物用EtOAc(50mL)稀释,用水及盐水分别洗涤3次。有机相经无水Na_2SO_4干燥,在减压下浓缩。通过C18急骤色谱纯化粗产物,得到呈浅棕色油状的(2S)-4-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-甲酸叔丁酯(140mg,56%)。

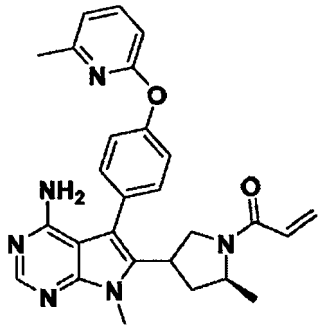
[1373] 7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-6-((5S)-5-甲基吡咯烷-3-基)-

7H-吡咯并[2,3-d]嘧啶-4-胺

[1374] 

[1375] 步骤8:向圆底烧瓶中装入(2S)-4-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-甲酸叔丁酯(140mg,272μmol)、TFA/DCM(1:4V/V,15mL)及搅拌棒。在室温下搅拌溶液3小时。移除溶剂且粗产物用DCM稀释且用Na2CO3水溶液调节至pH 7。浓缩有机相,得到7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-6-[(5S)-5-甲基吡咯烷-3-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(90.0mg,100%),其不经纯化即用于下一步骤。

[1376] 1-((2S)-4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮

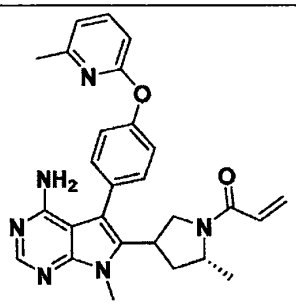
[1377] 

[1378] 步骤9:向圆底烧瓶中装入TEA(65.7mg,651μmol)、丙-2-烯酰氯(15.6mg,173μmol)、7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-6-[(5S)-5-甲基吡咯烷-3-基]-7H吡咯并[2,3-d]嘧啶-4-胺(90.0mg,217μmol)及搅拌棒。添加二氯甲烷(5mL),且在-65℃下搅拌溶液0.5小时。用MeOH淬灭混合物且浓缩。粗产物通过制备型HPLC纯化(柱:XBridge Shield RP18 OBD柱,30*150mm,5um;移动相A:水(10MMOL/L NH_4HCO_3),移动相B:ACN;流量:60mL/min;梯度:25B至50B,历时8分钟;220nm;RT1:7.23),得到呈白色固体状的1-[(2S)-4-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基]丙-2-烯-1-酮(38.3mg,38%)。

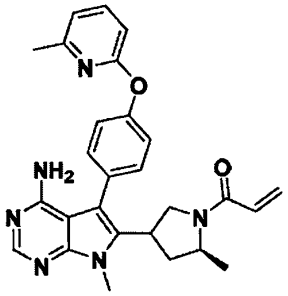
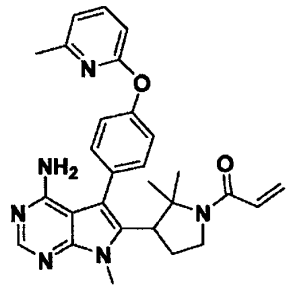
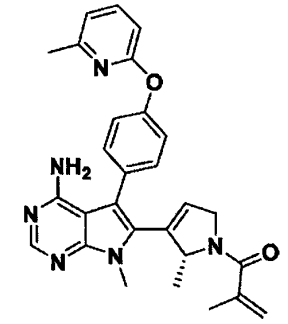
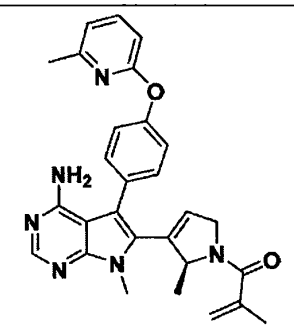
[1379] 根据实例15的方法制备的其它化合物描绘于下表14中。

[1380] 表14.其它示例性化合物

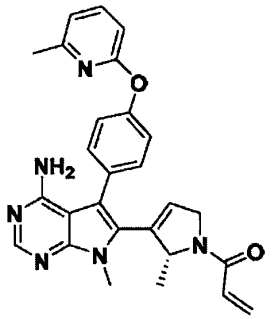
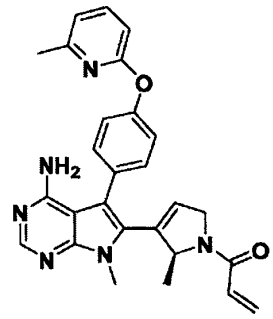
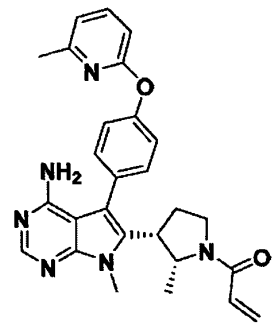
[1381]

化合物	结构	质子 NMR	MS [M+1]
1-((2R)-4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 7.4 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.50 (dd, J = 16.7, 10.4 Hz, 1H), 6.11 (t, J = 15.2 Hz, 1H), 5.62 (d, J = 10.7 Hz, 1H), 4.00 (s, 2H), 3.79 (s, 3H), 3.47 - 3.34 (m, J = 2.8 Hz, 1H), 2.32 (s, 4H), 1.65 (d, J = 9.8 Hz, 1H), 1.24 (s, 1H), 1.12 (d, J = 6.6 Hz, 3H).	469.40

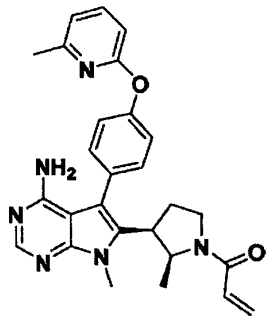
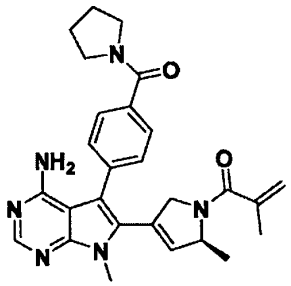
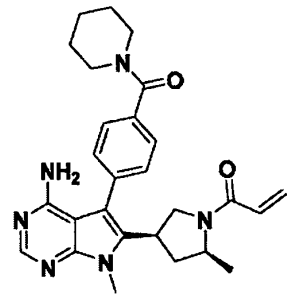
[1382]

化合物	结构	质子 NMR	MS [M+1]
1-((2S)-4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.27 - 7.18 (m, 2H), 7.03 (d = 7.3 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.64 - 6.43 (m, 1H), 6.17 - 6.07 (m, 1H), 5.75 - 5.38 (m, 2H), 4.24 - 3.94 (m, 2H), 3.79 (d, J = 3.8 Hz, 3H), 3.68 - 3.36 (m, 2H), 2.34 - 2.32 (m, 4H), 1.81 - 1.60 (m, 1H), 1.22 - 1.06 (m, 3H).	469.20
1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,2-二甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.17 (t, J = 8.8 Hz, 2H), 7.03 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.42 (dd, J = 16.5, 10.4 Hz, 1H), 6.03 (d, J = 16.6 Hz, 1H), 5.52 (d, J = 10.3 Hz, 1H), 3.80 (s, 3H), 3.61 (t, J = 8.6 Hz, 1H), 3.59(s, 1H), 2.33 (s, 3H), 2.15 (s, 2H), 1.46 (s, 3H), 1.16 (s, 4H).	483.40
(R)-1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基-2,5-二氢-1H-吡咯-1-基)-2-甲基丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.76 (dt, J = 12.1, 7.7 Hz, 1H), 7.44 - 7.37 (m, 2H), 7.23 (t, J = 5.3 Hz, 2H), 7.04 (t, J = 8.5 Hz, 1H), 6.82 (t, J = 9.7 Hz, 1H), 6.25 (d, J = 57.7 Hz, 1H), 5.94 (s, 2H), 5.33 - 4.74 (m, 2H), 4.57 - 4.19 (m, 3H), 3.75 (d, J = 4.7 Hz, 3H), 2.37 (s, 3H), 1.84 (s, 2H), 1.73 (s, 1H), 1.21 (d, J = 27.1 Hz, 1H), 0.96 (dd, J = 25.8, 6.3 Hz, 3H).	481.25
(S)-1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基-2,5-二氢-1H-吡咯-1-基)-2-甲基丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.76 (dt, J = 12.1, 7.8 Hz, 1H), 7.44 - 7.37 (m, 2H), 7.23 (dd, J = 8.8, 3.0 Hz, 2H), 7.04 (t, J = 8.5 Hz, 1H), 6.82 (t, J = 9.7 Hz, 1H), 6.24 (d, J = 57.7 Hz, 1H), 5.94 (s, 2H), 5.31 - 4.75 (m, 2H), 4.60 - 4.17 (m, 3H), 3.75 (d, J = 5.0 Hz, 3H), 2.37 (s, 3H), 1.79 (d, J = 45.3 Hz, 3H), 0.96 (dd, J = 26.0, 6.3 Hz, 3H).	481.25

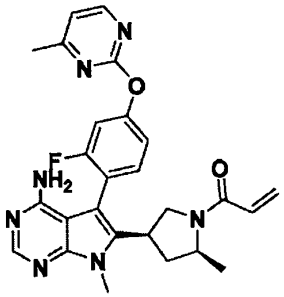
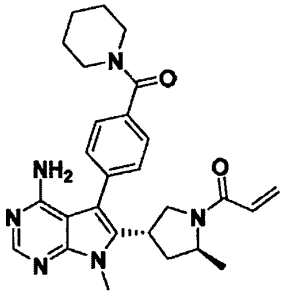
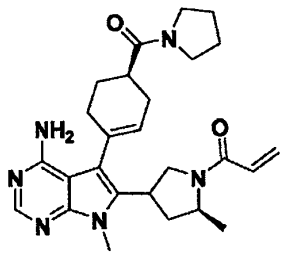
[1383]

化合物	结构	质子 NMR	MS [M+1]
(R)-1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基-2,5-二氢-1H-吡咯-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 2.0 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.22 (dd, J = 8.8, 2.3 Hz, 2H), 7.03 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.60 - 6.22 (m, 2H), 6.15 (ddd, J = 16.8, 5.1, 2.5 Hz, 1H), 5.97 (s, 2H), 5.66 (ddd, J = 22.4, 10.1, 2.5 Hz, 1H), 4.60 - 4.15 (m, 3H), 3.75 (d, J = 4.6 Hz, 3H), 2.36 (d, J = 8.8 Hz, 3H), 1.01 (dd, J = 6.2, 4.3 Hz, 3H).	467.25
(S)-1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基-2,5-二氢-1H-吡咯-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 2.0 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.22 (dd, J = 8.8, 2.3 Hz, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.55 (dd, J = 16.7, 10.3 Hz, 1H), 6.35 - 5.84 (m, 3H), 5.66 (ddd, J = 22.4, 10.2, 2.5 Hz, 1H), 4.60 - 4.14 (m, 3H), 3.75 (d, J = 4.6 Hz, 3H), 2.36 (d, J = 8.8 Hz, 3H), 1.01 (dd, J = 6.2, 4.4 Hz, 3H).	467.15
1-((2R,3R)-3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 0.9 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.40 (td, J = 5.7, 2.7 Hz, 2H), 7.19 (tt, J = 8.2, 2.2 Hz, 2H), 7.04 (dd, J = 7.4, 2.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.71 (dd, J = 16.6, 10.3 Hz, 1H), 6.51 (dd, J = 16.7, 10.3 Hz, 1H), 6.15-5.43 (ddd, J = 16.8, 12.1, 2.5 Hz, 2H), 4.55 (dp, J = 31.3, 6.6 Hz, 1H), 3.89 - 3.62 (m, 5H), 3.42 - 3.33 (m, 1H), 2.35 (d, J = 3.6 Hz,3H), 1.85 (dtd, J = 22.6, 12.4, 6.1 Hz, 2H), 0.83 (d, J = 6.5 Hz, 3H).	469.20

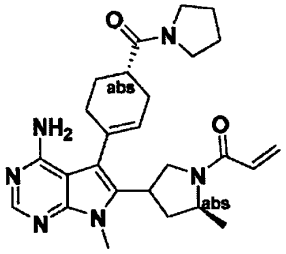
[1384]

化合物	结构	质子 NMR	MS [M+1]
1-((2S,3S)-3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.43 (t, J = 3.9 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.07 (dd, J = 8.1, 1.0 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.81 (dd, J = 8.0, 1.6 Hz, 1H), 6.67 (ddt, J = 21.6, 8.0, 4.6 Hz, 2H), 6.23 (dt, J = 16.8, 2.2 Hz, 1H), 6.05 (s, 1H), 5.76 (ddd, J = 10.3, 3.7, 2.3 Hz, 1H), 5.00 (s, 1H), 4.95 (s, 1H), 4.73 (d, J = 17.7 Hz, 2H), 3.62 (d, J = 1.7 Hz, 3H), 3.56 (s, 3H), 2.29 (d, J = 3.6 Hz, 3H).	533.40
(S)-1-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基-2,5-二氢-1H-吡咯-1-基)-2-甲基丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 7.7 Hz, 2H), 6.27 - 6.18 (m, 1H), 6.10 (s, 1H), 5.21 (d, J = 10.5 Hz, 1H), 5.07 (s, 1H), 4.89 (s, 1H), 4.17 - 4.03 (m, 1H), 3.98 (d, J = 14.4 Hz, 1H), 3.77 (s, 3H), 3.50 (t, J = 6.7 Hz, 2H), 3.44 (t, J = 6.4 Hz, 2H), 1.87 (dq, J = 17.8, 6.5 Hz, 5H), 1.70 (s, 2H), 1.26 (d, J = 6.4 Hz, 2H), 1.19 (d, J = 6.3 Hz, 1H).	471.30
1-((2S,4R)-4-(4-氨基-7-甲基-5-(4-(哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.48 (s, 4H), 6.52 (ddd, J = 27.6, 16.6, 10.2 Hz, 1H), 6.20 - 5.95 (m, 1H), 5.85 - 5.13 (m, 3H), 4.22 - 3.90 (m, 2H), 3.80 (s, 3H), 3.71 - 3.51 (m, 3H), 3.44 (t, J = 10.9 Hz, 1H), 3.14 (t, J = 11.7 Hz, 1H), 2.39 - 2.23 (m, 1H), 1.84 - 1.62 (m, 3H), 1.55 (t, J = 10.8 Hz, 5H), 1.06 (d, J = 6.3 Hz, 3H).	473.30

[1385]

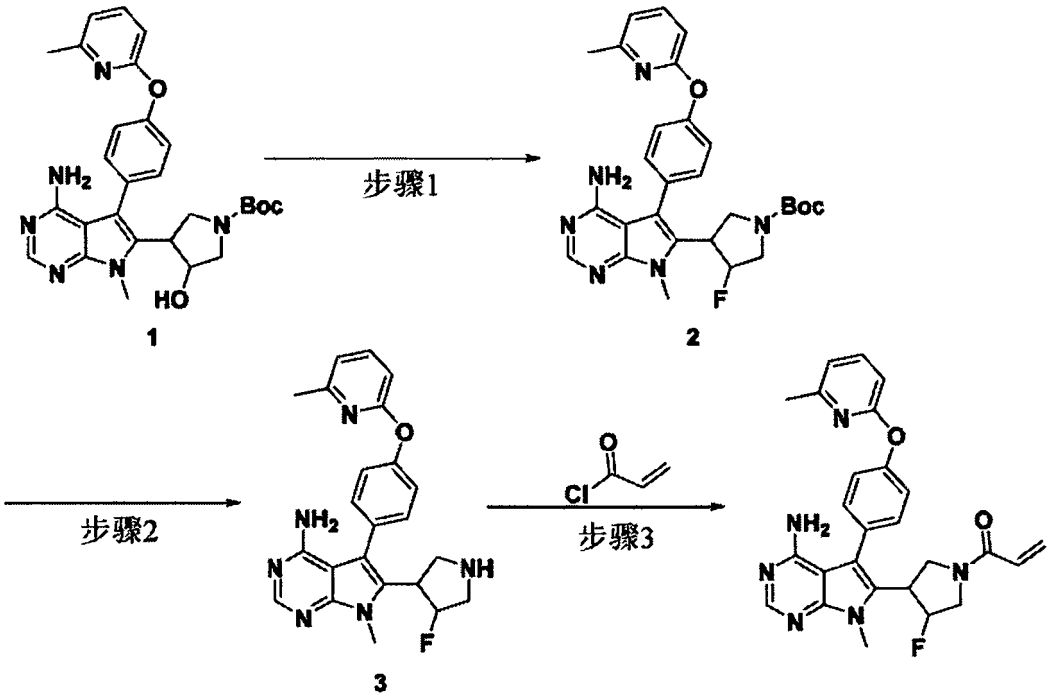
化合物	结构	质子 NMR	MS [M+1]
1-((2S,4R)-4-(4-氨基-5-(2-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 - 8.43 (m, 1H), 8.14 (s, 1H), 7.50 (td, J = 8.5, 3.8 Hz, 1H), 7.36 (ddt, J = 10.0, 4.8, 2.4 Hz, 1H), 7.27 - 7.13 (m, 2H), 6.75 - 6.41 (m, 1H), 6.19 - 5.98 (m, 1H), 5.80 - 5.33 (m, 3H), 4.36 - 3.91 (m, 2H), 3.80 (d, J = 4.0 Hz, 3H), 3.69 - 3.53 (m, 1H), 3.42 (dd, J = 20.4, 10.2 Hz, 1H), 2.42 (d, J = 8.0 Hz, 4H), 2.04 - 1.38 (m, 1H), 1.24 - 1.00 (m, 3H).	488.25
1-((2S,4S)-4-(4-氨基-7-甲基-5-(4-(哌啶-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 1.5 Hz, 1H), 7.45 (dd, J = 5.9, 3.0 Hz, 4H), 6.49 (ddd, J = 69.2, 16.7, 10.3 Hz, 1H), 6.11 (ddd, J = 16.4, 13.1, 2.5 Hz, 1H), 5.63 (ddd, J = 21.8, 10.2, 2.5 Hz, 3H), 4.22 (dt, J = 39.9, 7.0 Hz, 1H), 3.92 (dd, J = 15.7, 7.8 Hz, 2H), 3.79 (d, J = 11.1 Hz, 3H), 3.70 (dd, J = 12.5, 9.0 Hz, 1H), 3.56 (d, J = 17.7 Hz, 3H), 3.42 (d, J = 12.6 Hz, 1H), 2.37 - 2.06 (m, 1H), 1.95 (dd, J = 12.4, 6.8 Hz, 1H), 1.58 (d, J = 41.4 Hz, 6H), 1.24 (s, 1H), 1.14 (dd, J = 10.0, 6.4 Hz, 3H).	473.30
1-((2S)-4-(4-氨基-7-甲基-5-((R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 16.1 Hz, 1H), 6.63 (ddd, J = 26.2, 16.6, 10.2 Hz, 1H), 6.46 (s, 1H), 6.16 (td, J = 16.7, 2.6 Hz, 1H), 5.88 - 5.49 (m, 2H), 4.44 - 3.96 (m, 2H), 3.67 (d, J = 5.2 Hz, 4H), 3.52 (q, J = 8.8, 7.4 Hz, 3H), 3.32 (d, J = 5.6 Hz, 2H), 2.94 (s, 1H), 2.43 (d, J = 6.3 Hz, 1H), 2.37 - 2.19 (m, 3H), 2.18 - 1.99 (m, 2H), 1.89 (q, J = 6.6 Hz, 3H), 1.80 (h, J = 8.1, 7.0 Hz, 3H), 1.27 (dt, J = 18.0, 6.3 Hz, 3H).	463.30

[1386]

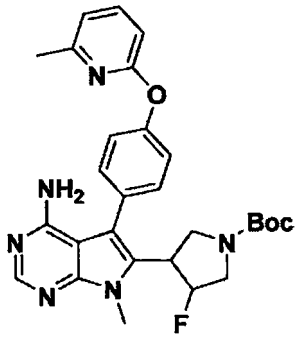
化合物	结构	质子 NMR	MS [M+1]
1-((2S)-4-(4-氨基-7-甲基-5-((S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-甲基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 16.7 Hz, 1H), 6.64 (td, J = 16.7, 10.5 Hz, 1H), 6.49 (s, 1H), 6.28 - 6.03 (m, 1H), 5.87 - 5.58 (m, 2H), 4.16 (d, J = 74.3 Hz, 2H), 3.67 (d, J = 4.2 Hz, 4H), 3.53 (s, 3H), 3.31 (s, 2H), 2.94 (s, 1H), 2.33 (s, 1H), 2.27 (s, 4H), 1.89 (q, J = 6.7 Hz, 4H), 1.80 (q, J = 6.7 Hz, 3H), 1.27 (dd, J = 21.1, 7.7 Hz, 3H).	463.35

[1387] 实例16

[1388] 流程13

[1389] 

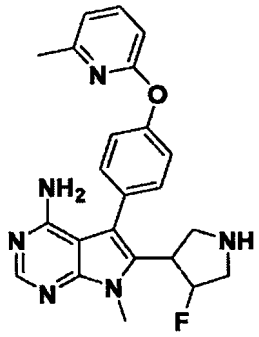
[1390] 3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-氟吡咯烷-1-甲酸叔丁酯

[1391] 

[1392] 步骤1:向圆底烧瓶中装入3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-甲酸叔丁酯(200mg,0.39mmol)、DCM(10mL)及搅拌棒。添加DAST(74.8mg,0.46mmol),且在0℃下搅拌溶液3小时。反应混合物用

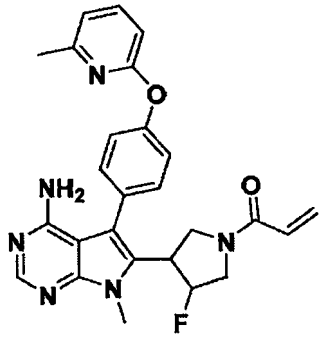
水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色固体状的3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-氟吡咯烷-1-甲酸叔丁酯(127mg,63%)。

[1393] 6-(4-氟吡咯烷-3-基)-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1394] 

[1395] 步骤2:向可再密封的反应瓶中装入3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-氟吡咯烷-1-甲酸叔丁酯(127mg,0.24mmol)、DCM(5mL)及搅拌棒。添加TFA(2mL),且在25℃下搅拌溶液1小时。浓缩反应混合物,用水稀释,用饱和Na2CO3将pH值调节至7,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过制备型TLC纯化。真空浓缩,产生呈棕色固体状的6-(4-氟吡咯烷-3-基)-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(77mg,77%)。

[1396] 1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-氟吡咯烷-1-基)丙-2-烯-1-酮

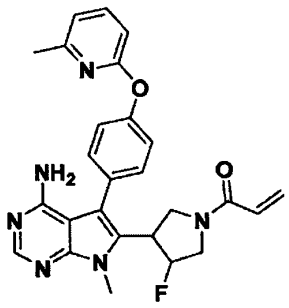
[1397] 

[1398] 步骤3:向圆底烧瓶中装入6-(4-氟吡咯烷-3-基)-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(77mg,180μmol)、TEA(55.8mg,0.55mmol)、DCM(5mL)及搅拌棒,添加丙烯酰氯(13.2mg,147μmol),且在-35℃下搅拌溶液0.5小时。反应混合物用MeOH淬灭,浓缩所得混合物,通过制备型HPLC纯化粗物质。冻干得到呈白色无定形固体状的1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-氟吡咯烷-1-基)丙-2-烯-1-酮(5.2mg,6%)。

[1399] 根据实例16的方法制备的其它化合物描绘于下表15中。

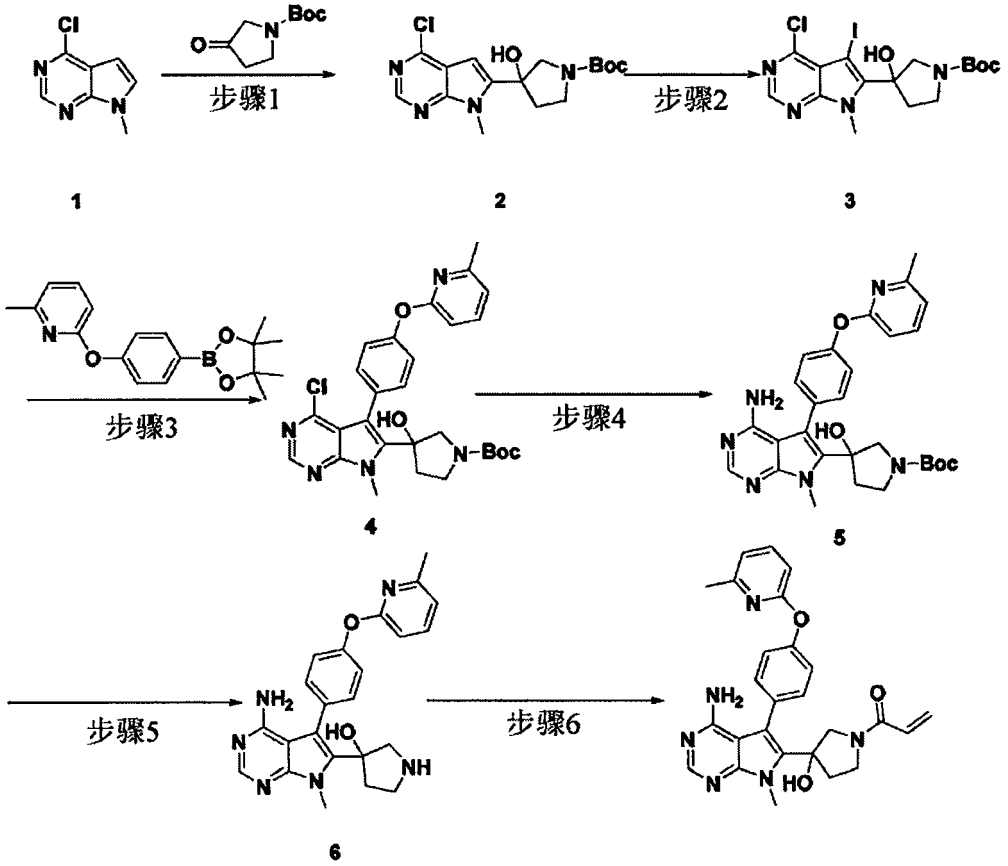
[1400] 表15.其它示例性化合物

[1401]

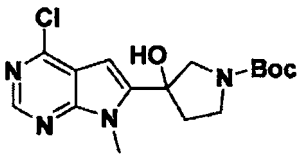
化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-氟吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.76 (td, J = 7.8, 4.4 Hz, 1H), 7.42 (s, 3H), 7.18 (s, 2H), 7.06 (dd, J = 7.3, 2.7 Hz, 1H), 6.87 (t, J = 8.1 Hz, 1H), 6.38 (ddd, J = 50.2, 16.7, 10.3 Hz, 1H), 6.07 (dt, J = 16.7, 2.8 Hz, 1H), 5.62 (td, J = 10.1, 2.4 Hz, 1H), 5.46 (ddd, J = 52.8, 19.4, 4.3 Hz, 1H), 4.58 - 3.27 (m, 8H), 2.39 (d, J = 1.4 Hz, 3H).	473.20

[1402] 实例17

[1403] 流程14

[1404] 

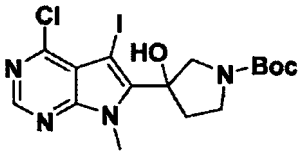
[1405] 3-(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯

[1406] 

[1407] 步骤1:向可再密封的反应瓶中装入4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶(5g,29.9mmol)、四氢呋喃(200mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在-78℃下逐滴添加LDA(30mL,59.9mmol),且在-78℃下搅拌混合物30分钟。逐滴添加存在于100mL THF中的3-侧氧基吡咯烷-1-甲酸叔丁酯(17g,89.8mmol),在-78℃下搅拌混合物1小时。使混合物升温至室温且反应混合物用H_2O(300mL)稀释,且水相用EA(300mL)萃取三次。合并的有机层用

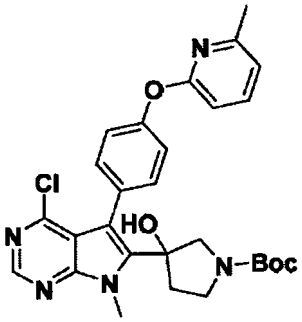
盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用PE/EA＝10/1洗脱)纯化。真空浓缩,产生呈淡黄色固体状的3-(4-氯-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(2.20g,20.9%)。

[1408] 3-(4-氯-5-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯

[1409] 

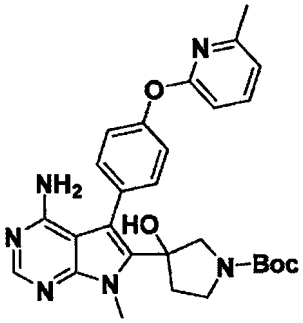
[1410] 步骤2:向圆底烧瓶中装入3-{4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3-羟基吡咯烷-1-甲酸叔丁酯(976mg,2.76mmol)、NIS(621mg,2.76mmol)、TFA(943mg,8.28mmol)及搅拌棒。添加DCM(20mL),且在室温下、在氮气保护下搅拌溶液3小时。混合物用饱和$Na_2S_2O_3$水溶液(10mL)淬灭,且用DCM(3*40mL)萃取,合并有机相且经无水Na_2SO_4干燥,在减压下浓缩,通过C18 Flash纯化粗产物,得到呈白色固体状的3-{4-氯-5-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3-羟基吡咯烷-1-甲酸叔丁酯(980mg,73.9%)。

[1411] 3-(4-氯-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯

[1412] 

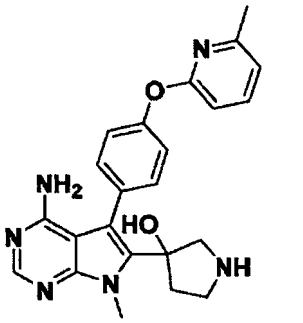
[1413] 步骤3:向可再密封的反应瓶中装入3-{4-氯-5-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3-羟基吡咯烷-1-甲酸叔丁酯(800mg,1.67mmol)、2-甲基-6-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]吡啶(519mg,1.67mmol)、Pd(PPh3)2Cl2(175mg,250μmol)、K3PO4(1.06g,5.01mmol)及搅拌棒。添加DMF/H2O(25mL),且在50℃下搅拌溶液1小时。混合物用EtOAc(100mL)稀释且用水(3*50mL)洗涤,浓缩有机相且粗产物通过C18 flash纯化且通过使用EA:PE＝2:1的制备型TLC进一步纯化,得到呈淡黄色固体状的3-(4-氯-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(140mg,15.6%)。

[1414] 3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯

[1415] 

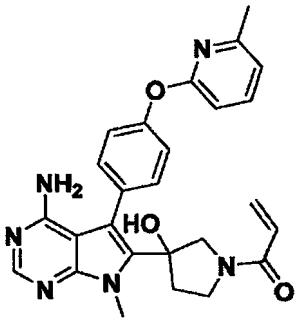
[1416] 步骤4:向可再密封的反应瓶中装入3-(4-氯-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(120mg,223μmol)、NH3H2O(1.82g,52.0mmol)及搅拌棒。添加二恶烷(1.5mL),将管密封且在100℃下搅拌溶液10小时。浓缩混合物且通过C18 flash纯化粗产物,得到呈浅黄色油状的3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(62.4mg,54.2%)。

[1417] 3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-醇

[1418] 

[1419] 步骤5:向圆底烧瓶中装入3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(80.0mg,154μmol)、TFA(52.6mg,462μmol)及搅拌棒。添加DCM(25mL),且在室温下搅拌溶液5小时。混合物用水稀释,且用Na_2CO_3调节pH至7,混合物用DCM(8*40mL)萃取,浓缩有机相且粗产物3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-醇(60.0mg,93.6%)不经纯化即用于下一步骤。

[1420] 1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-基)丙-2-烯-1-酮

[1421] 

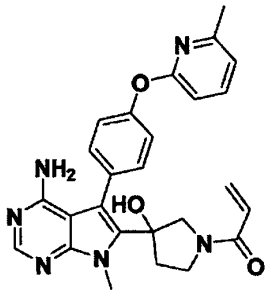
[1422] 步骤6:向圆底烧瓶中装入3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-醇(40mg,96.0μmol)、TEA(29.0mg,288μmol)、

DCM(15mL)及搅拌棒。添加丙-2-烯酰氯(6.95mg,76.8μmol,3.4mL),且在-45℃下搅拌溶液0.5小时。混合物用MeOH淬灭,且移除溶剂,粗产物通过HPLC纯化(柱:XBridge Prep OBD C18柱,19*250mm,5um),得到呈白色固体状的1-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-基]丙-2-烯-1-酮(10.5mg,23.2%)。

[1423] 根据实例17的方法制备的化合物的特征数据提供于下表16中。

[1424] 表16.示例性化合物

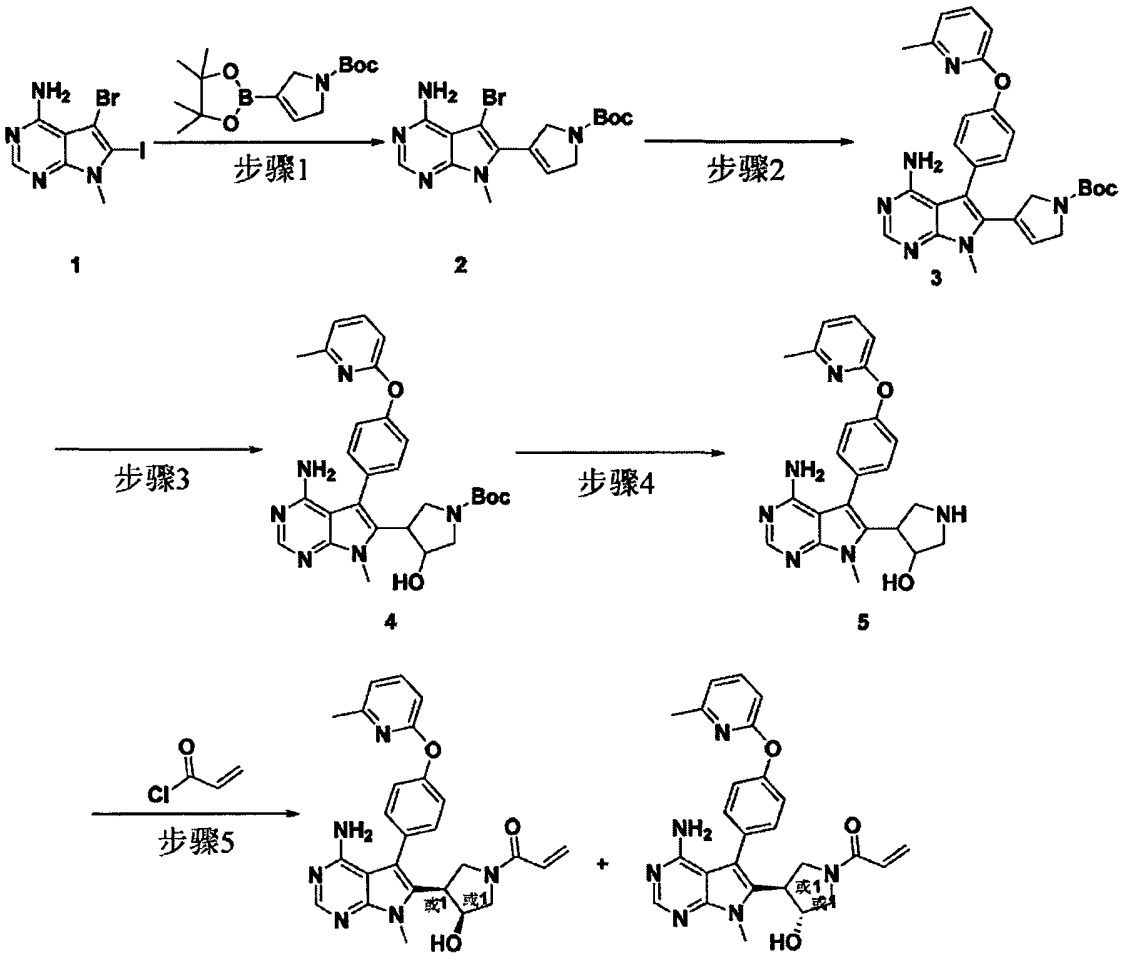
[1425]

化合物	结构	质子 NMR	MS [M+1]
1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.52 - 7.43(m, 2H), 7.24 - 7.21(m, 2H), 7.04 (dd, J = 7.4, 1.9 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.61 - 6.25 (m, 1H), 6.15 - 6.05(m, 1H), 5.88 - 5.83 (m, 1H), 5.65 - 5.59 (m, 1H), 3.96 (d, J = 4.9 Hz, 3H), 3.89 - 3.81 (m, 1H), 3.69 - 3.53 (m, 1H), 3.47 - 3.41 (m, 1H), 3.29 - 3.22 (m, 1H), 2.36 - 2.30 (m, 3H), 2.21 - 2.10 (m, 1H), 2.16 - 1.88 (m, 1H).	471.20

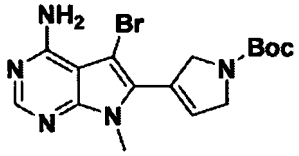
[1426] 实例18

[1427] 流程15

[1428]

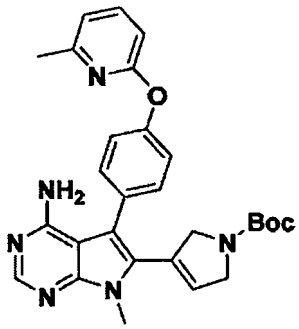


[1429] 3-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯

[1430] 

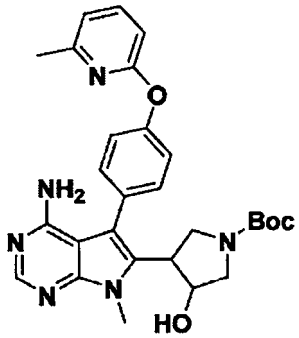
[1431] 步骤1:向圆底烧瓶中装入5-溴-6-碘-7-甲基吡咯并[2,3-d]嘧啶-4-胺(3g,8.50mmol)、3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-2,5-二氢吡咯-1-甲酸叔丁酯(3.01g,10.20mmol)、Pd(PPh3)4(982mg,850μmol)、K3PO4(5.41g,25.5mmol)及搅拌棒。添加二甲基甲酰胺/水(40mL,v/v=16:1),且在50℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色固体状的3-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(2g,60%)。

[1432] 3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯

[1433] 

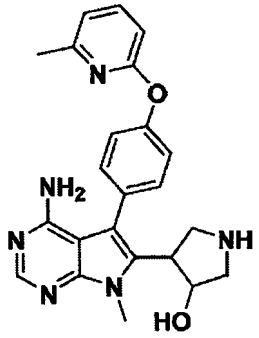
[1434] 步骤2:向可再密封的反应瓶中装入3-[4-氨基-5-溴-7-甲基吡咯并[2,3-d]嘧啶-6-基]-2,5-二氢吡咯-1-甲酸叔丁酯(600mg,1.52mmol)、2-甲基-6-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]吡啶(568mg,1.83mmol)、Pd(DtBPF)Cl2(99mg,152μmol)、K3PO4(0.97g,4.56mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF:水=16:1(10mL),且在90℃下搅拌溶液3小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈灰白色固体状的3-(4-氨基-7-甲基-5-[4-[(6-甲基吡啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢吡咯-1-甲叔丁酸酯(510mg,67%)。

[1435] 3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-甲酸叔丁酯

[1436] 

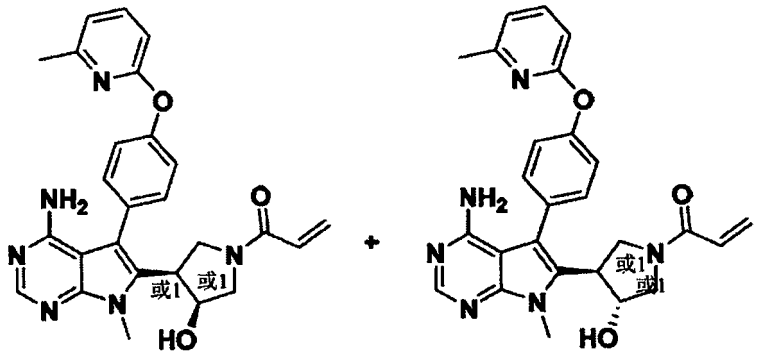
[1437] 步骤3:向圆底烧瓶中装入3-(4-氨基-7-甲基-5-[4-[(6-甲基吡啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-2,5-二氢吡咯-1-甲酸叔丁酯(450mg,0.90mmol)、THF(10mL)及搅拌棒。在0℃下添加BH3-THF(9.03mL,9.03mmol,1M于THF中),且在室温下搅拌溶液2小时。然后添加NaOH(9.03mL,9.03mmol,1M于H2O中)及H2O2(0.21mL,30%于水中)且再搅拌2小时。反应混合物用水淬灭,且用HCl(2M)调节pH值至7,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈棕色无定形固体状的3-(4-氨基-7-甲基-5-[4-[(6-甲基吡啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-甲酸叔丁酯(160mg,34%)。

[1438] 4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-醇

[1439] 

[1440] 步骤4:向可再密封的反应瓶中装入3-(4-氨基-7-甲基-5-[4-[(6-甲基吡啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-甲酸叔丁酯(160mg,0.31mmol)、DCM(5mL)及搅拌棒。添加TFA(2mL),且在25℃下搅拌溶液1小时。浓缩反应混合物,用水稀释,用饱和Na2CO3将pH值调节至7,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过制备型TLC纯化。真空浓缩,产生呈棕色固体状的4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-醇(100mg,78%)。

[1441] 1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-基)丙-2-烯-1-酮

[1442] 

1 2

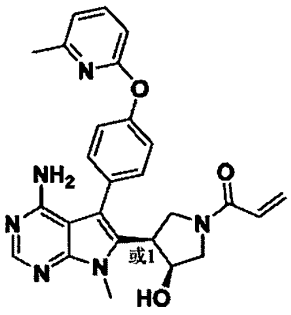
[1443] 步骤5:向圆底烧瓶中装入4-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-醇(82mg,170μmol)、TEA(52.8mg,0.52mmol)、DCM(5mL)及搅拌棒。添加丙烯酰氯(12.8mg,142μmol),且在-35℃下搅拌溶液0.5小时。反应混合物用MeOH淬灭,浓缩所得混合物,粗物质通过制备型HPLC纯化(柱:Xselect CSH OBD柱30*150mm 5um,n;移动相A:水(0.1%FA),移动相B:ACN;流量:60mL/min;梯度:5B至27B,历

时7分钟;220nm;RT1:6.10,6.80;RT2)。冻干得到1-(3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-基)丙-2-烯-1-酮(47.4mg,57%),包括:呈白色无定形固体状的1(19.1mg),及呈白色固体状的2(28.3mg)。

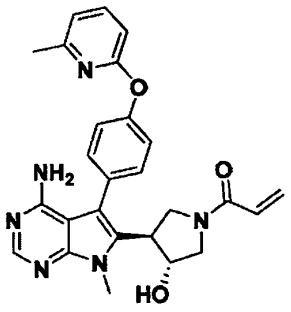
[1444] 根据实例18的方法制备的其它化合物描绘于下表17中。

[1445] 表17.其它示例性化合物

[1446]

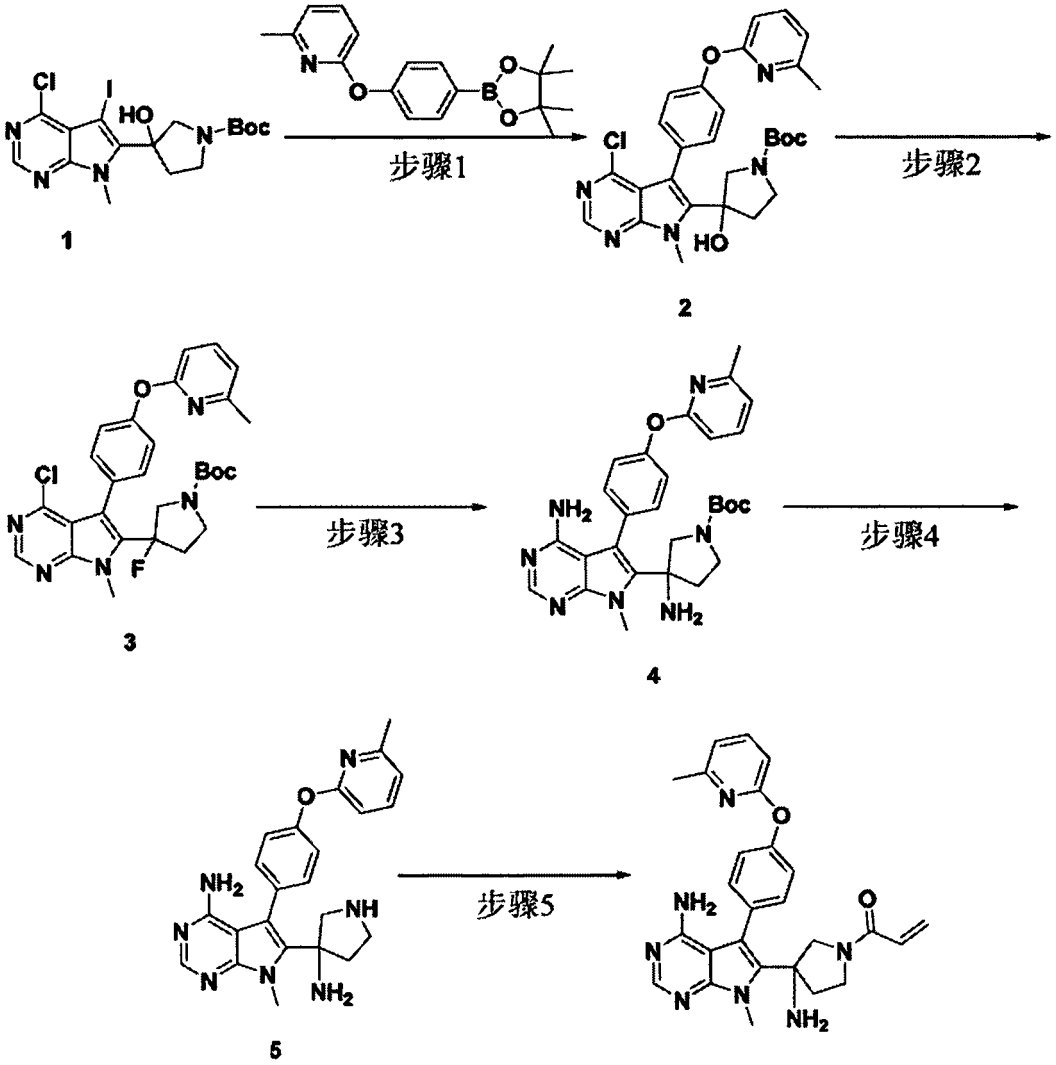
化合物	结构	质子 NMR	MS [M+1]
1-((3R,4S)-3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.76 (td, J = 7.8, 3.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.85 (t, J = 7.1 Hz, 1H), 6.41 (ddd, J = 59.1, 16.7, 10.2 Hz, 1H), 6.18 - 5.98 (m, 1H), 5.62 (t, J = 11.2 Hz, 1H), 4.42 (dd, J = 18.5, 7.3 Hz, 1H), 4.05 - 3.89 (m, 3H), 3.76 (s, 3H), 3.42 - 3.08 (m, 2H), 2.38 (s, 3H).	471.30

[1447]

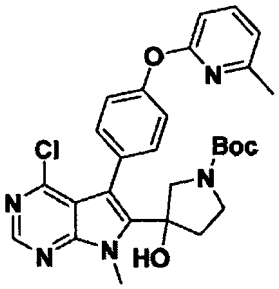
化合物	结构	质子 NMR	MS [M+1]
1-((3R,4R)-3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-4-羟基吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 2.1 Hz, 1H), 7.77 (td, J = 7.8, 3.7 Hz, 1H), 7.49 (ddd, J = 9.4, 6.7, 2.9 Hz, 2H), 7.34 - 7.18 (m, 2H), 7.06 (dd, J = 7.3, 2.4 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.43 (ddd, J = 104.5, 16.8, 10.3 Hz, 1H), 6.18 - 5.90 (m, 2H), 5.63 (ddd, J = 26.1, 10.2, 2.4 Hz, 1H), 4.05 (d, J = 4.3 Hz, 3H), 3.93 - 3.78 (m, 1H), 3.71 - 3.22 (m, 3H), 2.38 (d, J = 11.5 Hz, 3H), 2.34 - 2.10 (m, 1H), 2.00 (dt, J = 38.0, 10.5 Hz, 1H).	471.30

[1448] 实例19

[1449] 流程16

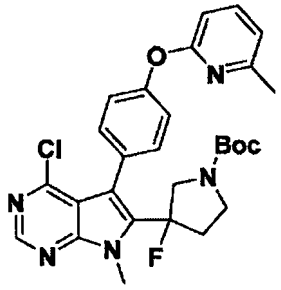
[1450] 

[1451] 3-(4-氯-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯

[1452] 

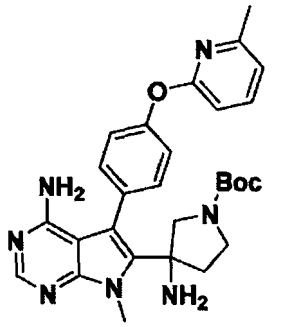
[1453] 步骤1:向可再密封的反应瓶中装入3-(4-氯-5-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(700mg,1.46mmol)、2-甲基-6-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]吡啶(546mg,1.75mmol)、Pd(PPh3)2C12(102mg,146μmol)、K3P04(929mg,4.38mmol)及搅拌棒。添加DMF/H20(25mL),且在50℃下搅拌溶液1小时。混合物用EtOAc(100mL)稀释,且用水(3*50mL)洗涤,浓缩有机相且粗产物通过C18 flash纯化且通过使用EA:PE=2:1的制备型TLC进一步纯化,得到呈淡黄色固体状的3-(4-氯-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(100mg,18.7%)。

[1454] 3-(4-氯-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟吡咯烷-1-甲酸叔丁酯

[1455] 

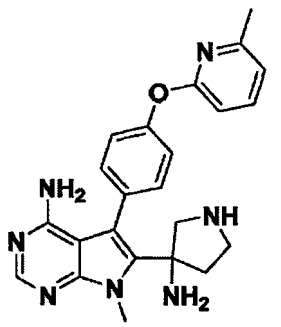
[1456] 步骤2:向圆底烧瓶中装入3-(4-氯-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-羟基吡咯烷-1-甲酸叔丁酯(90.0mg,167μmol)、DAST(4.00mg,24.8μmol)及搅拌棒。添加二氯甲烷(10mL),且在室温下搅拌溶液2小时。混合物用NaHCO3水溶液(10mL)淬灭且用DCM(30mL)萃取3次,浓缩有机相,通过制备型TLC(PE:EA=1:1)纯化粗产物,得到呈棕色固体状的3-(4-氯-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟吡咯烷-1-甲酸叔丁酯(40.0mg,44%)。

[1457] 3-氨基-3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲酸叔丁酯

[1458] 

[1459] 步骤3:向密封管中装入3-(4-氯-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟吡咯烷-1-甲酸叔丁酯(40.0mg,74.3μmol)、NH3H2O/1,4-二恶烷(46mL,v/v=1:1)及搅拌棒,将管密封且在100℃下搅拌混合物18小时。浓缩混合物且通过C18 FLASH纯化粗产物,得到呈黄色油状的3-氨基-3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲酸叔丁酯(26.0mg,68%)。

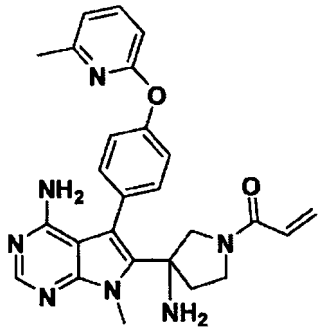
[1460] 6-(3-氨基吡咯烷-3-基)-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1461] 

[1462] 步骤4:向可再密封的反应瓶中装入、向圆底烧瓶中装入3-氨基-3-(4-氨基-7-甲

基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-甲酸叔丁酯(26.0mg,50.4μmol)、TFA/DCM(5mL,v/v=1:2)及搅拌棒,在室温下搅拌溶液2小时。浓缩混合物且通过C18 FLASH纯化粗产物,得到呈黄色油状的3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-胺(15.0mg,72%)。

[1463] 1-(3-氨基-3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮

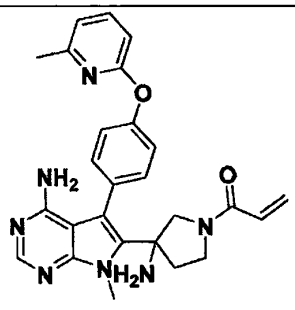
[1464] 

[1465] 步骤5:向圆底烧瓶中装入3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-3-胺(15.0mg,36.1μmol)、丙-2-烯酰氯(2.60mg,28.8μmol)、TEA(10.9mg,108μmol)及搅拌棒。添加二氯甲烷(1mL),且在-65℃下搅拌溶液0.5小时。混合物用MeOH淬灭,且在减压下浓缩,粗产物通过HPLC纯化(柱:XBridge Shield RP18 OBD柱,30*150mm,5um;移动相A:未定义;移动相B:未定义;流量:60mL/min;梯度:2B至22B,历时8分钟;220nm),得到呈白色固体状的1-[3-氨基-3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基]丙-2-烯-1-酮(3.00mg,18%)。

[1466] 根据实例19的方法制备的化合物的特征数据提供于下表18中。

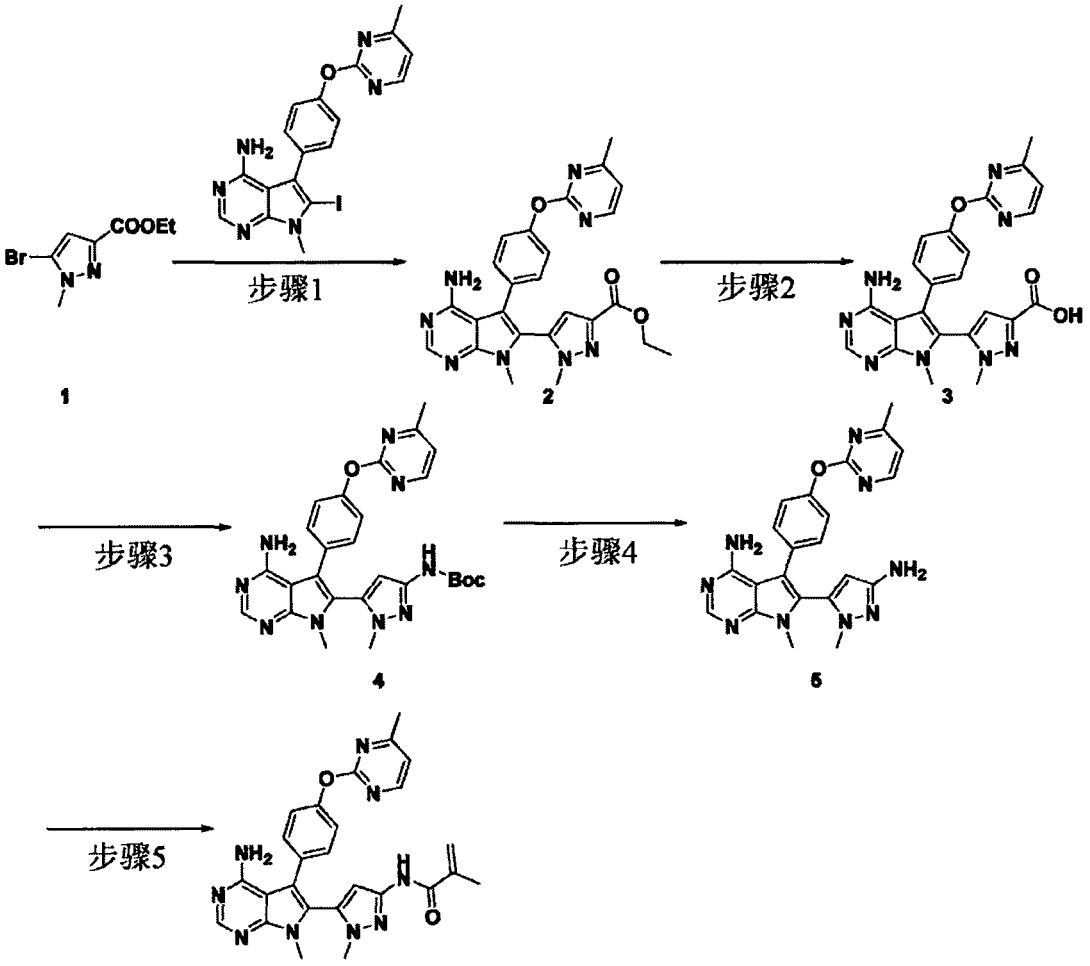
[1467] 表18.示例性化合物

[1468]

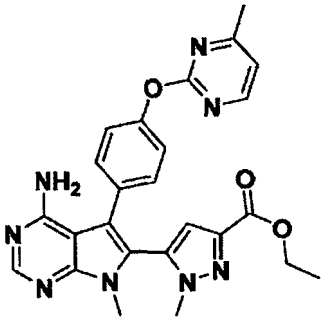
化合物	结构	质子 NMR	MS [M+1]
1-(3-氨基-3-(4-氨基-7-甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡咯烷-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.80 - 7.74 (m, 1H), 7.58 - 7.46 (m, 2H), 7.26 - 7.15 (m, 2H), 7.04 (dd, J = 7.4, 3.6 Hz, 1H), 6.89 - 6.82 (m, 1H), 6.58 - 6.51 (m, 1H), 6.28 - 6.17 (m, 1H), 6.14 - 6.03 (m, 1H), 5.66 - 5.54 (m, 1H), 4.00 (d, J = 4.5 Hz, 3H), 3.80 - 3.57 (m, 2H), 3.53 - 3.37 (m, 2H), 2.44 - 2.24 (m, 4H), 2.17 - 1.95 (m, 2H).	470.25

[1469] 实例20

[1470] 流程17

[1471] 

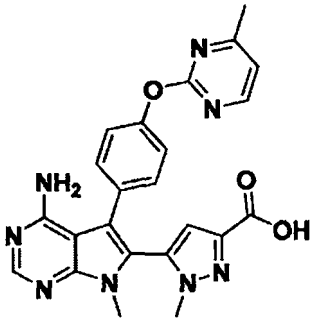
[1472] 5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-甲酸乙酯

[1473] 

[1474] 步骤1:向圆底烧瓶中装入4,4,4′,4′,5,5,5′,5′-八甲基-2,2′-双(1,3,2-二氧杂硼杂环戊烷)(610mg,2.4mmol)、5-溴-1-甲基-1H-吡唑-3-甲酸乙酯(464mg,2mmol)、6-碘-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(916mg,2mmol)、K3PO4(1.27g,6mmol)、DMF/H2O(8:1,10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物4小时。冷却后,混合物用水稀释,用DCM萃取,经Na_2SO_4干燥,真空蒸发,残余物通过C18柱色谱来纯化(移动相A:水(0.05%TFA),移动相B:ACN;流量:30mL/min;梯度:0B%至45B%,历时25分钟;254nm;),得到呈灰白色固体状的5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-甲酸乙酯(100mg,10%)。

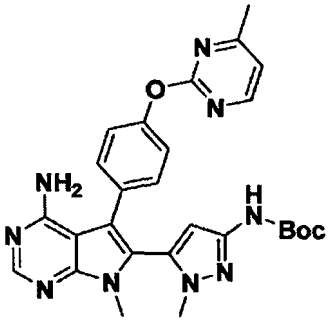
[1475] 5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧

啶-6-基)-1-甲基-1H-吡唑-3-甲酸

[1476] 

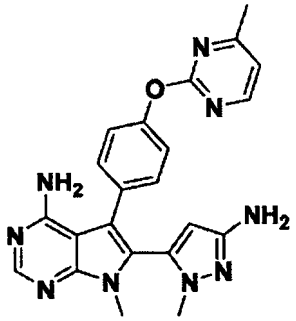
[1477] 步骤2:向圆底烧瓶中装入5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-甲酸乙酯(550mg,1.14mmol)、NaOH(136mg,3.40mmol)、MeOH(10mL)、H2O(5mL)及搅拌棒。在室温下搅拌混合物1小时。混合物在减压下浓缩,且用HCl(1N)调节pH至3,过滤且在减压下干燥,得到呈灰白色固体状的5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-甲酸(350mg,67%)。

[1478] (5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-基)氨基甲酸叔丁酯

[1479] 

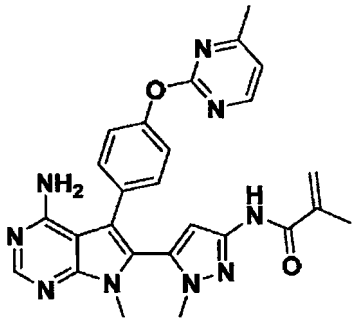
[1480] 步骤3:向圆底烧瓶中装入5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-甲酸(310mg,0.68mmol)、DPPA(280mg,1.02mmol)、TEA(138mg,1.36mmol)、DMSO/tBuOH(1:2,24mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物4小时。冷却后,混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空蒸发,残余物通过C18柱色谱纯化(移动相A:水(0.05%TFA),移动相B:ACN;流量:30mL/min;梯度:0B%至60B%,历时35分钟;254nm;),得到呈灰白色固体状的(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-基)氨基甲酸酯(60mg,8.3%)。

[1481] 6-(3-氨基-1-甲基-1H-吡唑-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1482] 

[1483] 步骤4:向圆底烧瓶中装入2-氯-4-甲基嘧啶(60mg,0.11mmol)、TFA(0.4mL)、DCM(4mL)及搅拌棒。在室温下搅拌反应混合物1小时。浓缩混合物且用DCM(20mL)溶解,用饱和NaHCO3水溶液及盐水洗涤,经Na_2SO_4干燥,真空蒸发,残余物通过C18柱色谱纯化(移动相A:水(0.05%TFA),移动相B:ACN;流量:30mL/min;梯度:0B%至60B%,历时35分钟;254nm;),得到呈黄色固体状的6-(3-氨基-1-甲基-1H-吡唑-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(35mg,74%)。

[1484] N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-基)甲基丙烯酰胺

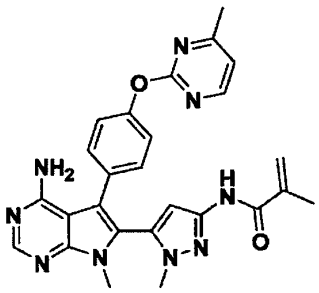
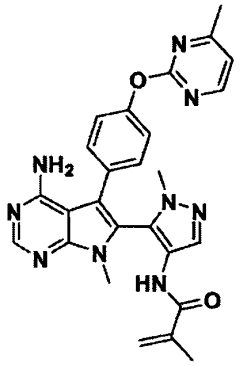
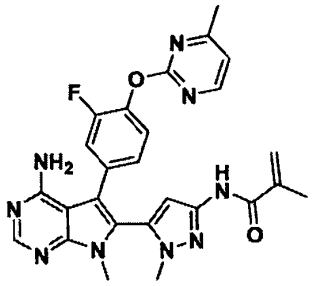
[1485] 

[1486] 步骤5:向圆底烧瓶中装入6-(3-氨基-1-甲基-1H-吡唑-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(70mg,0.16mmol)、Na2CO3(34mg,0.32mmol)、ACN(20mL)及搅拌棒。在-30℃下逐滴添加甲基丙烯酰氯(14.6mg,0.14mmol),且搅拌混合物1小时。混合物然后在-30℃下用MeOH淬灭,且用水(10mL)稀释,用DCM(20mL*3)萃取,合并有机相且用盐水洗涤两次,经Na_2SO_4干燥,真空浓缩,通过HPLC纯化残余物且冻干,得到呈白色固体状的N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-基)甲基丙烯酰胺(12-5mg,15%)。

[1487] 根据实例20的方法制备的其它化合物描绘于下表19中。

[1488] 表19-其它示例性化合物

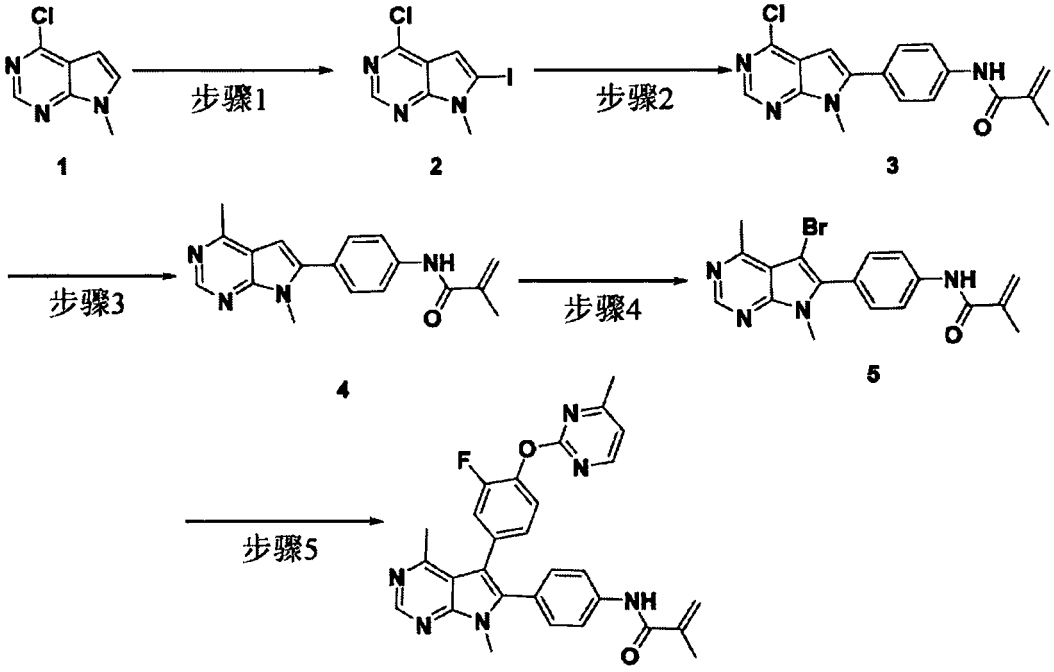
[1489]

化合物	结构	质子 NMR	MS [M+1]
N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.48(d, J = 4.2 Hz, 1H), 8.25 (s, 1H), 7.31 (d, J = 8.4 Hz, 2H),7.24 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 4.2 Hz, 1H), 6.84 (s, 1H), 5.87(s,1H), 5.49 (s, 1H), 3.59(s, 3H), 3.27(s, 3H),2.41(s, 3H), 1.93(s, 3H).	496.10
N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-4-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.47(d, J = 4.8 Hz, 1H), 8.24 (s, 1H), 7.72(s, 1H), 7.37 (d, J = 8.4 Hz, 2H),7.22 - 7.15 (m, 3H), 5.60(s,1H), 5.41 (s, 1H), 3.51(s, 3H), 3.27(s, 3H),2.41(s, 3H), 1.92(s, 3H).	496.15
N-(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-1-甲基-1H-吡唑-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 7.41 (t, J = 8.4 Hz, 1H), 7.23 - 7.18 (m, 2H), 7.11 (m, 1H), 6.87 (s, 1H), 6.25 (s, 1H), 5.88 (s, 1H), 5.54 - 5.46 (s, 1H), 3.59 (s, 3H), 3.30 (s, 3H), 2.42 (s, 3H), 1.94 (s, 3H).	514.20

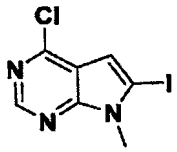
[1490] 实例21

[1491] 流程18

[1492]

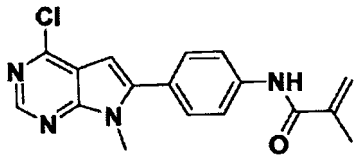


[1493] 4-氯-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶

[1494] 

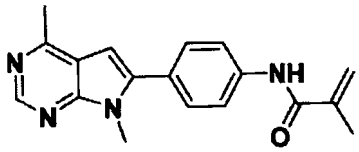
[1495] 步骤1:向三颈烧瓶中装入4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶(3g,17.96mmol)、THF(50mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在约-78℃下逐滴添加LDA(13.5mL,26.9mmol)。在约-78℃下搅拌反应混合物1小时。然后添加I_2(5.9g,23.3mmol),在-78℃下搅拌反应混合物1小时。混合物用水淬灭,用EA萃取,经Na_2SO_4干燥,真空蒸发,通过硅胶柱色谱(用DCM/MeOH(50:1至10:1)洗脱)来纯化残余物,得到呈黄色固体状的4-氯-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶(4g,76%)。

[1496] N-(4-(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

[1497] 

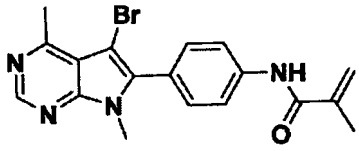
[1498] 步骤2:向圆底烧瓶中装入4-氯-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶(1g,3.4mmol)、N-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)甲基丙烯酰胺(1.2g,4.1mmol)、Pd(PPh3)2Cl_2(4.5g,6.2mmol)、K3PO4(2.16g,10.2mmol)、DMF/H2O(16:1,20mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在50℃下搅拌混合物1小时。冷却后,混合物用水稀释,用EA萃取,经Na_2SO_4干燥,真空蒸发,残余物通过硅胶柱色谱(用DCM/MeOH(100:1至10:1)洗脱)来纯化,得到呈黄色固体状的N-(4-(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(700mg,70%)。

[1499] N-(4-(4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

[1500] 

[1501] 步骤3:向圆底烧瓶中装入N-(4-(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(0.7g,2.3mmol)、Pd(PPh3)4(0.26g,0.23mmol)、DMF(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加Zn(CH3)2(1M,3.45mL,3.45mmol)。在90℃下搅拌混合物2小时。冷却后,混合物用水稀释,用DCM萃取,经Na_2SO_4干燥,真空蒸发,通过硅胶柱色谱(用DCM/MeOH(100:1至10:1)洗脱)纯化残余物,得到呈棕色固体状的N-(4-(4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(400mg,57%)。

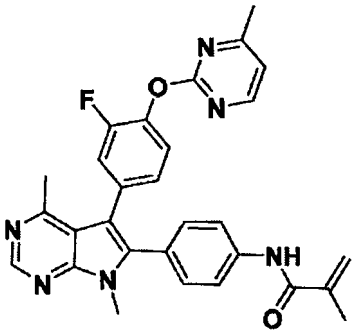
[1502] 6-碘-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1503] 

[1504] 步骤4:向圆底烧瓶中装入N-(4-(4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺(0.4g,1.3mmol)、DCM(10mL)及搅拌棒。添加NBS(7.43g,1.3mmol)。搅拌混

合物1小时。反应物用饱和$NaHSO_3$水溶液淬灭直至pH至8-9,用DCM(100mL*3)萃取,合并有机相且用盐水洗涤两次,经Na_2SO_4干燥,真空蒸发,残余物用ACN(25mL)溶解且过滤,滤饼用ACN洗涤,在减压下干燥,得到呈灰白色固体状的6-碘-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(340mg,67%)。

[1505] N-(4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺

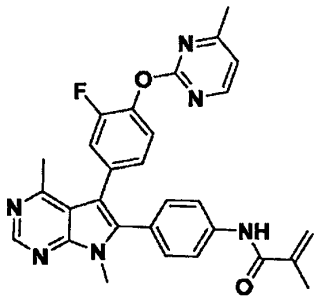
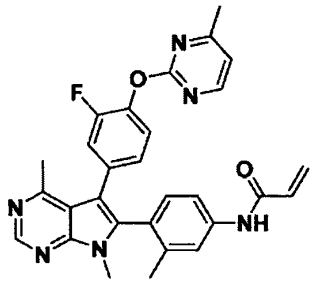
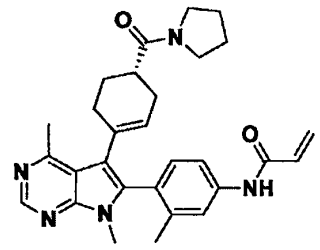
[1506] 

[1507] 步骤5:向圆底烧瓶中装入6-碘-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(340mg,0.88mmol)、2-(2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基)-4-甲基嘧啶(330mg,1mmol)、Pd(dppf)Cl_2(66mg,0.09mmol)、K3PO4(560mg,2.64mmol)、DMF/H2O(16:1,10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物2小时。冷却后,混合物用水稀释,用DCM萃取,经Na_2SO_4干燥,真空蒸发,通过制备型HPLC纯化残余物,得到呈白色固体状的6-(4-氨基苯基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(46.6mg,10.4%)。

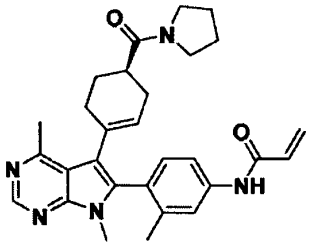
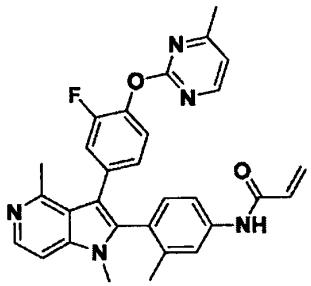
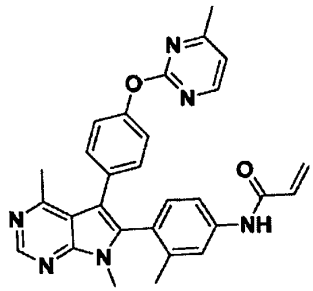
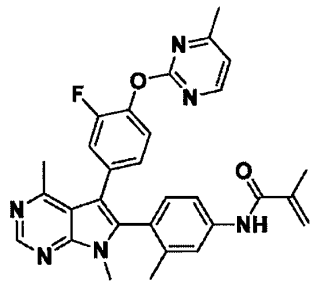
[1508] 根据实例21的方法制备的其它化合物描绘于下表20中。

[1509] 表20.其它示例性化合物

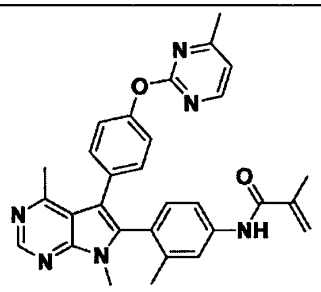
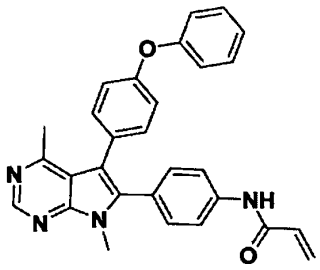
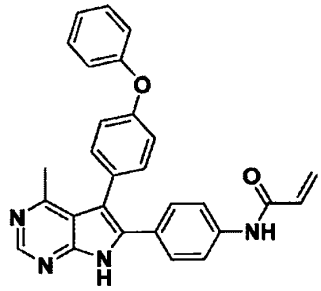
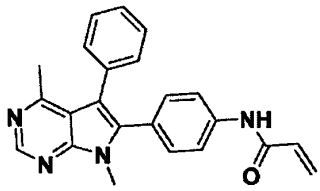
[1510]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.74 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 7.80 - 7.74 (m, 2H), 7.41 - 7.26 (m, 4H), 7.22 - 7.11 (m, 2H), 5.80 (s, 1H), 5.54 (t, J = 1.5 Hz, 1H), 3.70 (s, 3H), 2.40 (d, J = 11.0 Hz, 6H), 1.95 (d, J = 1.2 Hz, 3H).	509.20
N-(4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6)10.24 (s, 1H), 8.74 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 7.66-7.57 (m, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.33-7.24 (m, 2H), 7.17 (d, J = 5.1 Hz, 1H), 7.16-7.10 (m, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.52 (s, 3H), 2.41 (d, J = 8.1 Hz, 6H), 2.00 (s, 3H).	509.35
(S)-N-(4-(4,7-二甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6)10.27 (s, 1H), 8.65 (s, 1H), 7.71 (dd, J = 4.9, 2.1 Hz, 1H), 7.66-7.58 (m, 1H), 7.24 (dd, J = 10.7, 8.3 Hz, 1H), 6.47 (dd, J = 17.0, 10.1 Hz, 1H), 6.29 (dd, J = 17.0, 2.1 Hz, 1H), 5.80 (dd, J = 10.1, 2.1 Hz, 1H), 5.66 (d, J = 14.9 Hz, 1H), 3.47-3.39 (m, 5H), 3.32 (s, 3H), 3.26 (t, J = 6.8 Hz, 2H), 2.65 (s, 3H), 2.27-2.16 (m, 1H), 2.07 (t, J = 3.8 Hz, 4H), 1.85 (p, J = 6.6 Hz, 2H), 1.74 (p, J = 6.5 Hz, 3H), 1.49-1.41 (m, 1H).	484.45

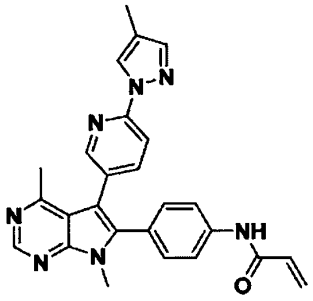
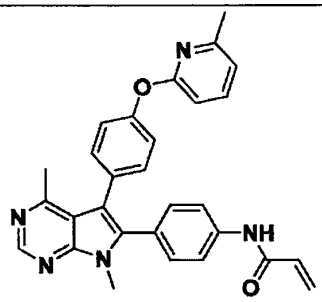
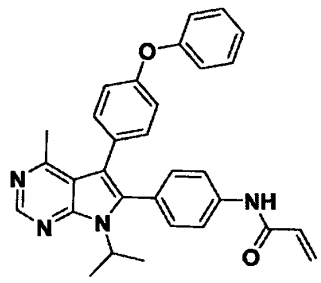
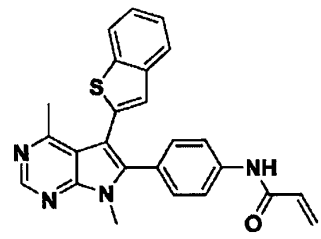
[1511]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4,7-二甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6)10.28 (s, 1H), 8.64 (s, 1H), 7.71 (dd, J = 5.1, 2.0 Hz, 1H), 7.62 (dt, J = 5.9, 3.2 Hz, 1H), 7.23 (dd, J = 10.6, 8.3 Hz, 1H), 6.47 (dd, J = 17.0, 10.1 Hz, 1H), 6.29 (dd, J = 17.0, 2.1 Hz, 1H), 5.79 (dd, J = 10.0, 2.0 Hz, 1H), 5.70-5.61 (m, 1H), 3.42 (s, 4H), 3.26 (t, J = 6.9 Hz, 2H), 2.65 (s, 3H), 2.18 (d, J = 10.3 Hz, 0H), 2.06 (d, J = 4.0 Hz, 4H), 1.85 (p, J = 6.7 Hz, 2H), 1.74 (p, J = 6.7 Hz, 3H), 1.45 (d, J = 12.9 Hz, 1H).	484.45
N-[4-(3-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-1,4-二甲基-1H-吡咯并[3,2-c]吡啶-2-基)-3-甲基苯基]丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.29 (s, 1H), 7.64 (s, 1H), 7.61 (s, 1H), 7.59 (s, 1H), 7.30 (dd, J = 12.2, 8.6 Hz, 3H), 7.15 (dd, J = 17.4, 6.6 Hz, 2H), 6.45 (dd, J = 16.9, 10.1 Hz, 1H), 6.36 - 6.09 (m, 1H), 5.78 (d, J = 11.8 Hz, 1H), 3.56 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H), 2.01 (s, 3H).	508.25
N-(4-(4,7-二甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6)10.22 (s, 1H), 8.73 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 7.64-7.55 (m, 2H), 7.36-7.26 (m, 3H), 7.17-7.08 (m, 3H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J =17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.52 (s, 3H), 2.39 (d, J = 4.4 Hz, 6H), 1.99 (s, 3H).	491.35
N-[4-(5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基]-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.74 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H), 7.65-7.61 (m, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.32-7.26 (m, 2H), 7.18 (d, J = 5.1 Hz, 1H), 7.16- 7.10 (m, 1H), 5.81 (t, J = 1.1 Hz, 1H), 5.54 (s, 1H), 3.52 (s, 3H), 2.41 (d, J = 7.5 Hz, 6H), 1.99 (s, 3H), 1.97 - 1.91 (m, 3H).	523.35

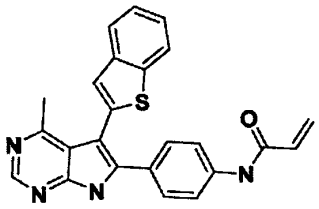
[1512]

化合物	结构	质子 NMR	MS [M+1]
N-[4-(4,7-二甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基]-2-甲基丙-2-烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.73 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.50 - 7.27 (m, 3H), 7.18 - 6.92 (m, 3H), 5.80 (t, J = 1.0 Hz, 1H), 5.53 (d, J = 1.9 Hz, 1H), 3.52 (s, 3H), 2.39 (d, J = 4.6 Hz, 6H), 1.98 (s, 3H), 1.95 (d, J = 1.3 Hz, 3H).	505.35
N-(4-(4,7-二甲基-5-(4-苯氧基苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.72 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.46-7.32 (m, 2H), 7.30 (s, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 7.07-7.00 (m, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.45 (dd, J = 16.9, 10.1 Hz, 1H), 6.28 (dd, J = 17.1, 2.0 Hz, 0H), 5.79 (dd, J = 10.1, 2.0 Hz, 1H), 3.70 (s, 3H), 2.34 (s, 3H).	461.30
N-(4-(4-甲基-5-(4-苯氧基苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.52 (t, J = 6.1 Hz, 1H), 8.22-7.98 (m, 4H), 7.96-7.76 (m, 4H), 7.42 (t, J = 7.8 Hz, 1H), 7.37-7.26 (m, 1H), 7.12 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.29 (dd, J = 17.1, 10.1 Hz, 1H), 6.14 (dd, J = 17.1, 2.3 Hz, 1H), 5.62 (dd, J = 10.0, 2.4 Hz, 1H), 4.28 (d, J = 5.9 Hz, 2H), 3.50 (s, 3H), 3.18 (s, 4H), 3.05 (s, 2H).	447.30
N-(4-(4,7-二甲基-5-苯基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.71 (s, 1H), 7.72-7.64 (m, 2H), 7.38-7.25 (m, 7H), 6.43 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.0, 2.1 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 3H).	369.20

[1513]

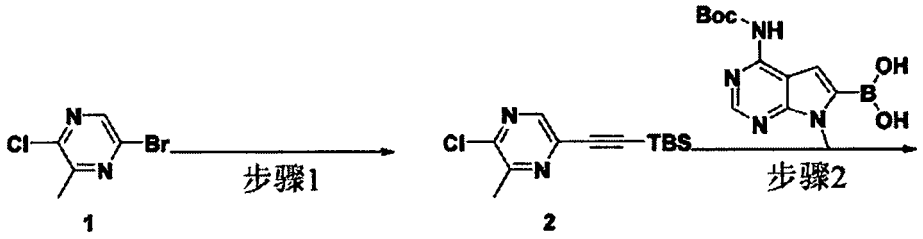
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4,7-二甲基-5-(6-(4-甲基-1H-吡唑-1-基)吡啶-3-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.75 (s, 1H), 8.37 (t, J = 1.0 Hz, 1H), 8.29 (dd, J = 2.3, 0.8 Hz, 1H), 7.90 (dd, J = 8.4, 2.3 Hz, 1H), 7.84 (dd, J = 8.4, 0.8 Hz, 1H), 7.76-7.69 (m, 2H), 7.65 (s, 1H), 7.42-7.34 (m, 2H), 6.43 (dd, J = 16.9, 10.0 Hz, 1H), 6.27 (dd, J = 17.0, 2.1 Hz, 1H), 5.78 (dd, J = 10.1, 2.1 Hz, 1H), 3.72 (s, 3H), 2.39 (s, 3H), 2.11 (d, J = 1.0 Hz, 3H).	450.30
N-(4-(4,7-二甲基-5-(4-((6-甲基吡啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.72 (s, 1H), 7.78-7.69 (m, 3H), 7.36 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.33-6.23 (m, 1H), 5.78 (d, J = 10.1 Hz, 1H), 3.71 (s, 3H), 2.34 (s, 6H).	476.15
N-(4-(7-异丙基-4-甲基-5-(4-苯氧基苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.69 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.41 (t, J = 7.8 Hz, 2H), 7.29 (dd, J = 16.6, 8.3 Hz, 4H), 7.16 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.2 Hz, 2H), 6.45 (dd, J = 16.9, 10.0 Hz, 1H), 6.29 (dd, J = 16.8, 1.9 Hz, 1H), 5.79 (dd, J = 10.2, 2.0 Hz, 1H), 4.43 (p, J = 6.8 Hz, 1H), 2.30 (s, 3H), 1.63 (d, J = 6.8 Hz, 6H).	489.15
N-(4-(5-(苯并[b]噻吩-2-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.77 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.86-7.79 (m, 1H), 7.75-7.68 (m, 2H), 7.52-7.43 (m, 3H), 7.42-7.29 (m, 2H), 6.42 (dd, J = 17.0, 10.1 Hz, 1H), 6.26 (dd, J = 16.9, 2.1 Hz, 1H), 5.77 (dd, J = 10.0, 2.1 Hz, 1H), 3.72 (s, 3H), 2.44 (s, 3H).	425.25

[1514]

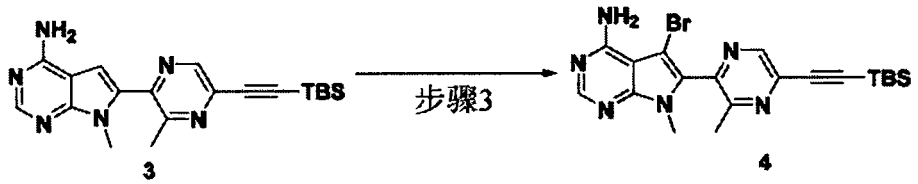
化合物	结构	质子 NMR	MS [M+1]
N-(4-(5-(苯并[b]噻吩-2-基)-4-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 10.25 (s, 1H), 8.68 (s, 1H), 8.05-7.95 (m, 1H), 7.89 (dd, J = 6.8, 1.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.57-7.49 (m, 3H), 7.45-7.35 (m, 2H), 6.41 (dd, J = 17.0, 10.1 Hz, 1H), 6.25 (dd, J = 17.0, 2.1 Hz, 1H), 5.77 (dd, J = 10.1, 2.1 Hz, 1H), 2.36 (s, 3H).	411.15

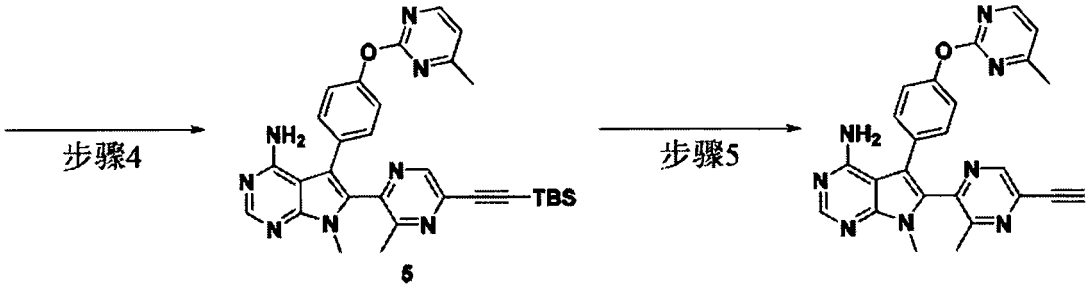
[1515] 实例22

[1516] 流程19



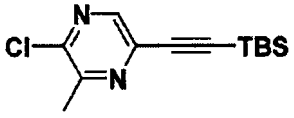
[1517]





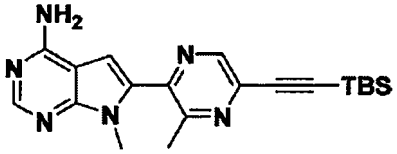
[1518] 5-[2-(叔丁基二甲基硅烷基)乙炔基]-2-氯-3-甲基吡嗪

[1519]



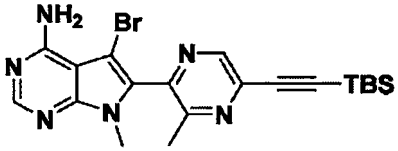
[1520] 步骤1:向圆底烧瓶中装入5-溴-2-氯-3-甲基吡嗪(1g,4.82mmol)、叔丁基(乙炔基)二甲基硅烷(810mg,5.78mmol)、Pd(PPh3)2C12(675mg,964μmol)、CuI(364mg,1.92mmol)、TEA(2.43g,24.1mmol)及搅拌棒。添加二甲基甲酰胺(20mL),且在50℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色油状的5-[2-(叔丁基二甲基硅烷基)乙炔基]-2-氯-3-甲基吡嗪(1g,77%)。

[1521] 6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1522] 

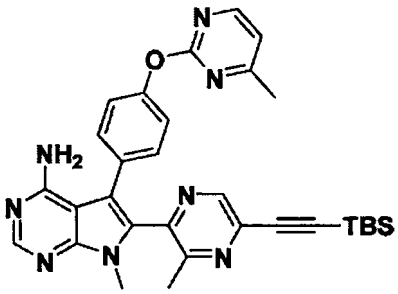
[1523] 步骤2:向可再密封的反应瓶中装入5-[2-(叔丁基二甲基硅烷基)乙炔基]-2-氯-3-甲基吡嗪(600mg,2.24mmol)、(4-{[(叔丁氧基)羰基]氨基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)硼酸(1.30g,4.48mmol)、G3-X-phos(189mg,224μmol)、Xphos(213mg,448μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷:水=16:1(20mL),且在90℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈灰白色无定形固体状的6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(600mg,70%)。

[1524] 5-溴-6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1525] 

[1526] 步骤3:向圆底烧瓶中装入6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,1.32mmol)、二甲基甲酰胺(5mL)及搅拌棒。添加NBS(234mg,1-32mmol),且在室温下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈灰白色无定形固体状的5-溴-6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,82%)。

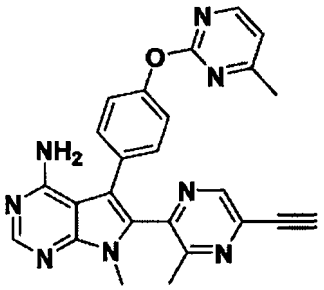
[1527] 6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺

[1528] 

[1529] 步骤4:向可再密封的反应瓶中装入4-甲基-2-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]嘧啶(374mg,1.20mmol)、5-溴-6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(460mg,1.00mmol)、Pd(dppf)Cl2(73.1mg,100μmol)、Cs2CO3(975mg,3.00mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷:水=16:1(10mL),且在90℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过制备型TLC纯化。真空浓缩,产生呈灰白色无定形固体状的6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,73%)。

[1530] 6-(5-乙炔基-3-甲基吡嗪-2-基)-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯

基}-7H-吡咯并[2,3-d]嘧啶-4-胺

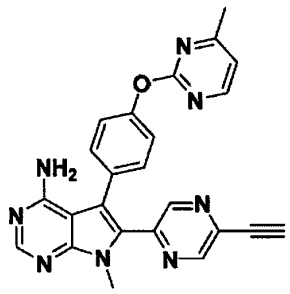
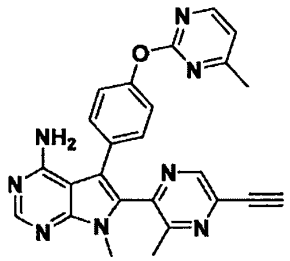
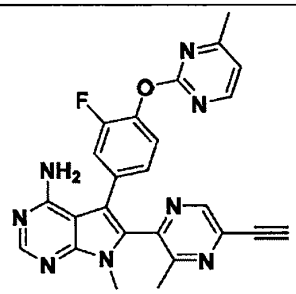
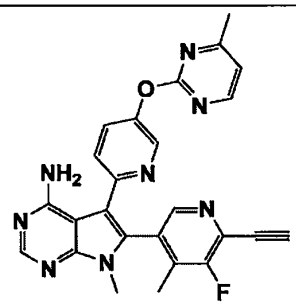
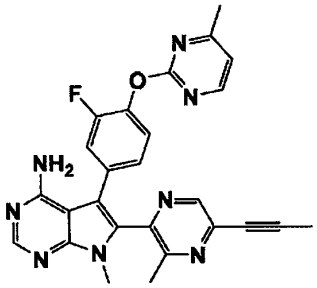
[1531] 

[1532] 步骤5:向圆底烧瓶中装入6-{5-[2-(叔丁基二甲基硅烷基)乙炔基]-3-甲基吡嗪-2-基}-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(480mg,852μmol)、CsF(387mg,2.55mmol)及搅拌棒。添加THF(10mL),且在50℃下搅拌溶液2小时。过滤反应混合物,用DCM洗涤,真空浓缩。所得粗物质通过制备型HPLC纯化。冻干产生呈灰白色无定形固体状的6-(5-乙炔基-3-甲基吡嗪-2-基)-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(260mg,68%)。

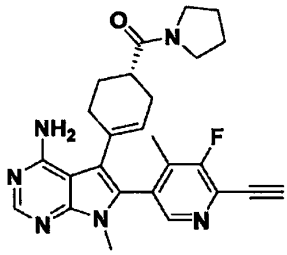
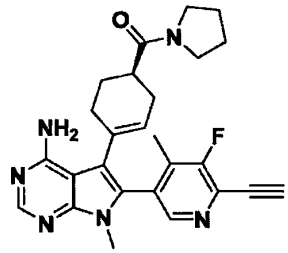
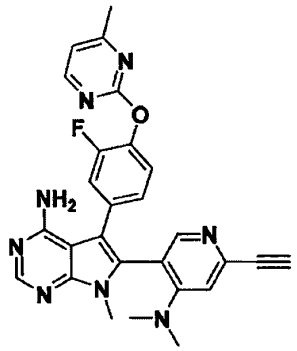
[1533] 根据实例22的方法制备的其它化合物描绘于下表21中。

[1534] 表21.其它示例性化合物

[1535]

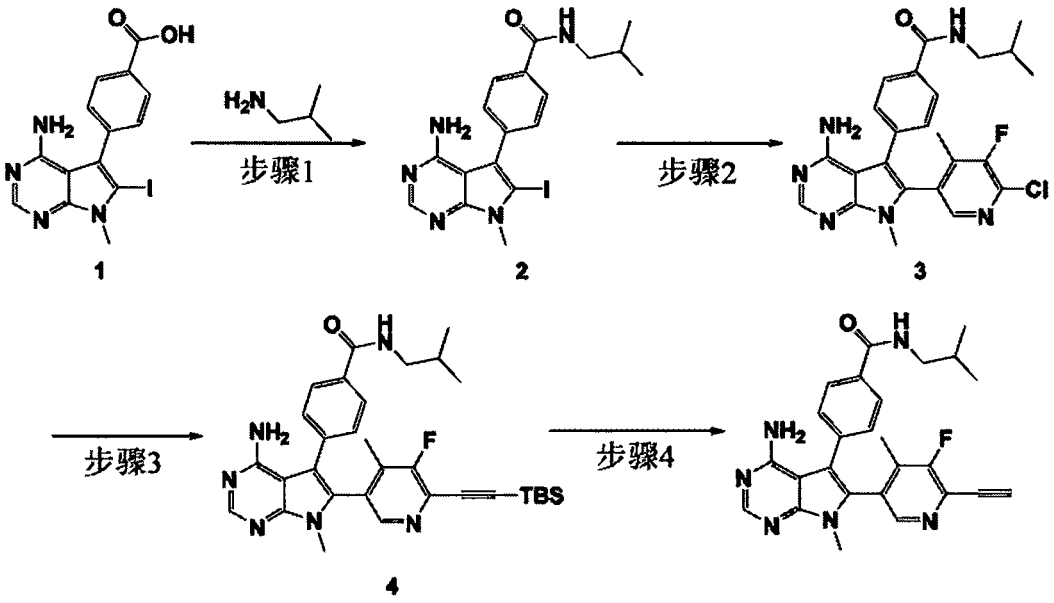
化合物	结构	质子 NMR	MS [M+1]
6-(5-乙炔基吡嗪-2-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (d, J = 1.5 Hz, 1H), 8.50 (d, J = 5.0 Hz, 1H), 8.29 - 8.20 (m, 2H), 7.43 - 7.33 (m, 2H), 7.33 - 7.23 (m, 2H), 7.18 (d, J = 5.0 Hz, 1H), 6.10 (s, 2H), 4.75 (s, 1H), 3.85 (s, 3H), 2.43 (s, 3H).	435.30
6-(5-乙炔基-3-甲基吡嗪-2-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) 8.81 (d, J = 0.8 Hz, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.20 -7.12 (m, 5H), 4.73 (s, 1H), 3.57 (s, 3H), 2.38 (s, 3H), 1.98 - 1.94 (m, 3H).	449.20
6-(5-乙炔基-3-甲基吡嗪-2-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.35 (s, 1H), 7.35 (t, J = 8.4 Hz, 2H), 7.20 (d, J = 5.0 Hz,2H), 7.08 (s, 1H), 6.92 (d, J = 7.9 Hz, 1H), 4.78 (s, 1H), 3.62 (s, 3H), 2.42 (s, 3H), 2.02 (s, 3H).	467.15
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 - 8.59 (m, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.43 (s, 1H), 8.21 (s, 1H), 7.52 (dd, J = 8.8, 2.8 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 6.88 - 6.81 (m, 1H), 4.86 (d, J = 0.8 Hz, 1H), 3.47 (s, 3H), 2.41 (s, 3H), 2.02 (d, J = 2.1 Hz, 3H).	467.30
5-(3-氟-4-(4-甲基嘧啶-2-基氧基)苯基)-7-甲基-6-(3-甲基-5-(丙-1-炔基)吡嗪-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) 8.72 (d, J = 0.8 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.11 (d, J = 11.2 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.27 (s, 1H), 3.58 (s, 3H), 2.42 (s, 3H), 2.16 (s, 3H), 2.00 (d, J = 0.6 Hz, 3H).	481.15

[1536]

化合物	结构	质子 NMR	MS [M+1]
(S)-(4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.29 (d, J = 7.0 Hz, 1H), 8.18 (s, 1H), 5.93 (s, 1H), 4.21 (dd, J = 1.9, 0.9 Hz, 1H), 3.63 - 3.50 (m, 2H), 3.51 (s, 3H), 3.49 - 3.37 (m, 2H), 2.85 (q, J = 6.1 Hz, 1H), 2.45 - 2.28 (m, 2H), 2.21 (dd, J = 3.7, 2.2 Hz, 3H), 2.18 - 2.01 (m, 2H), 2.03 - 1.95 (m, 2H), 1.92 - 1.85 (m, 2H), 1.77 (dt, J = 12.1, 6.1 Hz, 2H).	459.30
(R)-(4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.29 (d, J = 7.0 Hz, 1H), 8.18 (s, 1H), 5.83 (dd, J = 3.8, 1.9 Hz, 1H), 4.21 (dd, J = 1.9, 0.8 Hz, 1H), 3.55 (dtd, J = 10.2, 6.6, 3.6 Hz, 2H), 3.51 (s, 3H), 3.43 (ddt, J = 9.3, 6.5, 3.7 Hz, 2H), 2.86 (p, J = 6.2 Hz, 1H), 2.44 - 2.31 (m, 1H), 2.28 (s, 1H), 2.21 (dd, J = 3.7, 2.2 Hz, 3H), 2.12 (d, J = 14.2 Hz, 2H), 2.04 - 1.96 (m, 2H), 1.94 - 1.86 (m, 2H), 1.79 (p, J = 6.9, 6.4 Hz, 2H).	459.30
6-(4-(二甲基氨基)-6-乙炔基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 5.1 Hz, 1H), 8.22 (s, 1H), 8.06 (s, 1H), 7.36 (t, J = 8.4 Hz, 1H), 7.24 - 7.16 (m, 2H), 7.09 (d, J = 8.6 Hz, 1H), 6.91 (s, 1H), 6.14(s,1H), 4.25 (s, 1H), 3.54 (s, 3H), 2.63 (s, 6H), 2.42 (s, 3H).	495.20

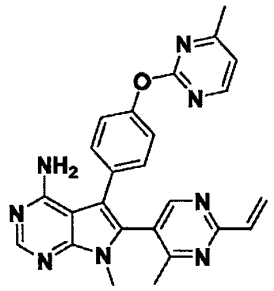
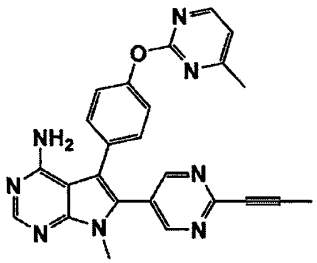
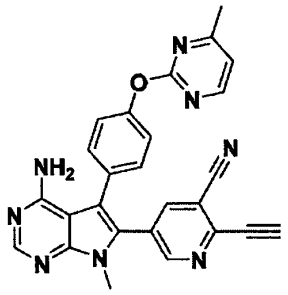
[1537] 实例23流程20

[1538]



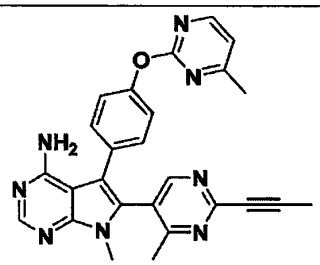
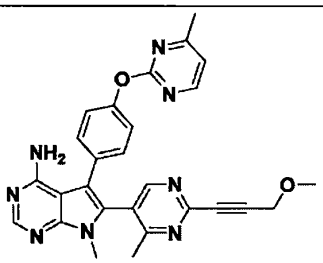
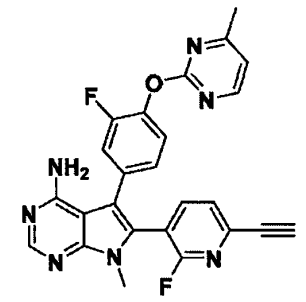
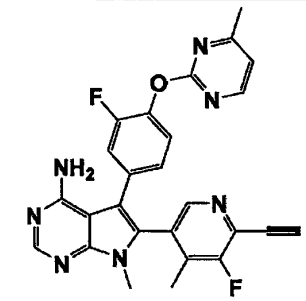
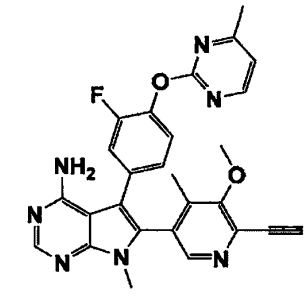
[1539] 根据实例23的方法制备的其它化合物描绘于下表22中。

[1540] 表22.其它示例性化合物

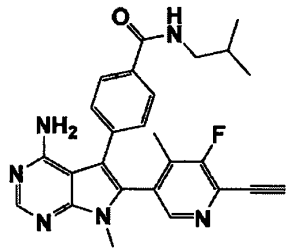
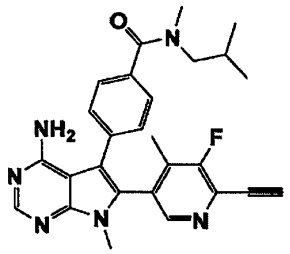
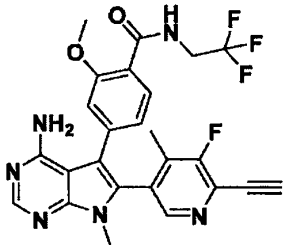
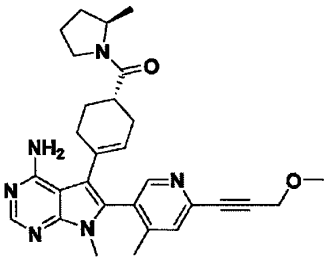
化合物	结构	质子 NMR	MS [M+1]
7-甲基-6-(4-甲基-2-乙烯基嘧啶-5-基)-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.46 (d, J = 5.1 Hz, 1H), 8.25 (s, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 5.0 Hz, 1H), 6.81 (d, J = 10.7 Hz, 1H),6.65 (d, J = 10.8 Hz, 1H), 5.82 (s, 1H), 3.54 (s, 3H), 2.40 (s, 3H), 2.17 (s, 3H).	451.10
7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(2-(丙-1-炔-1-基)嘧啶-5-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 2H), 8.48 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.38 - 7.31 (m, 2H), 7.29 - 7.18 (m, 2H), 7.17 (s, 1H), 5.89 (d, J = 103.6 Hz, 1H), 3.71 (s, 3H), 2.43 (s, 3H), 2.12 (s, 3H).	449.15
5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基烟腈		^{1}H NMR (400 MHz, DMSO-d_6) 8.63 (d, J = 2.2 Hz, 1H), 8.50 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.34-7.27 (m, 2H), 7.25-7.18 (m, 2H), 7.14 (d, J = 5.0 Hz, 1H), 5.03 (s, 1H), 3.68 (s, 3H), 2.40 (s, 3H).	459.10

[1541]

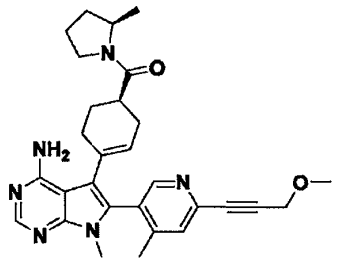
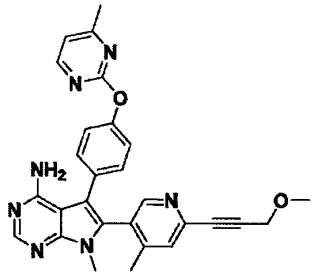
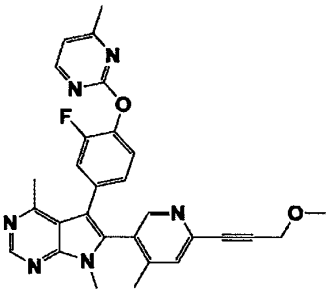
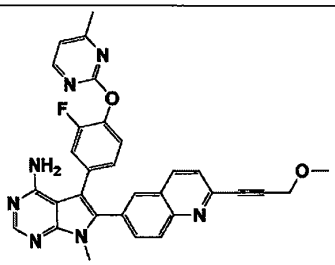
[1542]

化合物	结构	质子 NMR	MS [M+1]
7-甲基-6-(4-甲基-2-(丙-1-炔-1-基)嘧啶-5-基)-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.26 - 7.13 (m, 3H), 3.53 (s, 3H), 2.41 (s, 3H), 2.12 (d, J = 3.2 Hz, 6H).	463.35
6-(2-(3-甲氧基丙-1-炔-1-基)-4-甲基嘧啶-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.29 - 7.17 (m, 5H), 4.40 (s, 2H), 3.55 (s, 3H), 3.36 (d, J = 1.4 Hz, 3H), 2.41 (s, 3H), 2.14 (s, 3H).	493.15
6-(6-乙炔基-2-氟吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d_6) 8.49 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 8.08 (dd, J = 9.6, 7.6 Hz, 1H), 7.65 (dd, J = 7.5, 1.7 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.27 - 7.17 (m, 2H), 7.07 (d, J = 8.3 Hz, 1H), 4.64 (s, 1H), 3.60 (s, 3H), 2.42 (s, 3H), 2.08 (s, 1H).	470.25
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR(300 MHz, DMSO-d6) 8.47 (d, J = 5.0 Hz, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.24 - 7.12 (m, 2H), 7.03 (d, J = 9.4 Hz, 1H), 4.79 (s, 1H), 3.51 (s, 3H), 2.40 (s, 3H), 1.97 (d, J = 2.2 Hz, 3H).	484.35
6-(6-乙炔基-5-甲氧基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 8.24 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.20 - 7.12 (m, 2H), 7.04 - 6.98 (m, 1H), 6.18 (s, 2H), 4.63 (s, 1H), 3.83 (s, 3H), 3.51 (s, 3H), 2.40 (s, 3H), 1.91 (s, 3H).	496.30

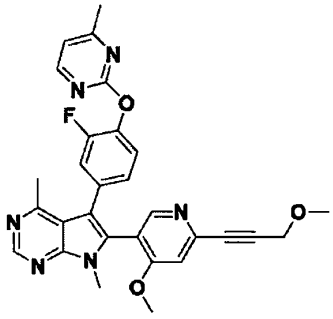
[1543]

化合物	结构	质子 NMR	MS [M+1]
4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-异丁基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.25 (s, 1H), 7.83 - 7.76 (m, 2H), 7.29 - 7.22 (m, 2H), 6.12 (s, 2H), 4.80 (s, 1H), 3.51 (s, 3H), 3.06 (t, J = 6.4 Hz, 2H), 1.94 (d, J = 2.1 Hz, 3H), 1.82 (dq, J = 13.3, 6.7 Hz, 1H), 0.88 (d, J = 6.7 Hz, 6H).	457.20
4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-异丁基-N-甲基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.25 (s, 1H), 7.41 - 7.26 (m, 2H), 7.22 (d, J = 7.6 Hz, 2H), 6.16 (s, 2H), 4.78 (s, 1H), 3.53 (d, J = 7.5 Hz, 3H), 3.29 (d, J = 11.4 Hz, 1H), 3.05 - 2.80 (m, 4H), 1.89 (d, J = 26.0 Hz, 4H), 0.93 (dd, J = 17.7, 7.0 Hz, 3H), 0.63 (s, 3H).	471.25
4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-甲氧基-N-(2,2,2-三氟乙基)苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) 8.62 (t, J = 6.4 Hz, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 6.92 (d, J = 1.5 Hz, 1H), 6.83 (dd, J = 7.9, 1.5 Hz, 1H), 6.21 (s, 1H), 4.81 (d, J = 0.8 Hz, 1H), 4.08 (td, J = 9.7, 6.6 Hz, 2H), 3.75 (s, 3H), 3.52 (s, 3H), 1.97 (d, J = 2.1 Hz, 3H).	513.35
((S)-4-(4-氨基-6-(6-(3-甲氧基丙-1-炔-1-基)-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 8.42 - 8.35 (m, 1H), 8.17 - 8.06 (m, 1H), 7.61 (d, J = 2.3 Hz, 1H), 6.67 (s, 2H), 5.69 (d, J = 36.7 Hz, 1H), 4.39 (s, 2H), 4.01 (t, J = 4.6 Hz, 1H), 3.45 (d, J = 6.6 Hz, 1H), 3.37 (s, 7H), 2.71 (d, J = 33.3 Hz, 1H), 2.24 (s, 1H), 2.18 - 2.03 (m, 4H), 2.00 - 1.42 (m, 8H), 1.13 - 1.01 (m, 3H).	499.30

[1544]

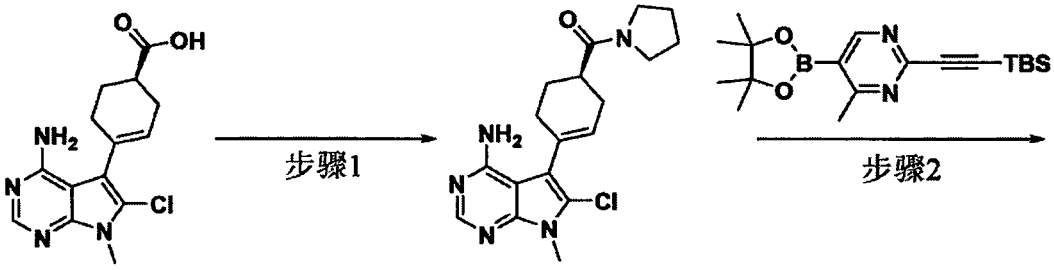
化合物	结构	质子 NMR	MS [M+1]
((R)-4-(4-氨基-6-(6-(3-甲氧基丙-1-炔-1-基)-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 8.47 - 8.34 (m, 1H), 8.13 (s, 1H), 7.61 (d, J = 2.2 Hz, 1H), 6.54 (s, 2H), 5.66 (d, J = 26.0 Hz, 1H), 4.39 (s, 2H), 4.04 (d, J = 37.4 Hz, 1H), 3.57 - 3.40 (m, 1H), 3.37 (s, 7H), 2.69 (s, 1H), 2.13 (d, J = 4.4 Hz, 5H), 2.05 - 1.42 (m, 8H), 1.08 (dd, J = 12.8, 6.5 Hz, 3H).	499.30
6-(6-(3-甲氧基丙-1-炔-1-基)-4-甲基吡啶-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.53 (s, 1H), 7.27 - 7.20 (m, 2H), 7.20 - 7.11 (m, 3H), 6.03 (s, 2H), 4.37 (s, 2H), 3.47 (s, 3H), 3.35 (s, 3H), 2.40 (s, 3H), 2.01 (s, 3H).	492.40
5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(6-(3-甲氧基丙-1-炔-1-基)-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.54 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 7.57 (s, 1H), 7.36 - 7.27 (m, 2H), 7.18 (d, J = 5.0 Hz, 1H), 7.17 - 7.09 (m, 1H), 4.38 (s, 2H), 3.57 (s, 3H), 3.35 (s, 3H), 2.41 (d, J = 9.6 Hz, 6H), 2.06 (s, 3H).	509.25
5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(2-(3-甲氧基丙-1-炔-1-基)喹啉-6-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.09 (d, J = 1.9 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.74 (dd, J = 8.7, 2.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.25 (dd, J = 11.3, 2.0 Hz, 1H), 7.20 - 7.11 (m, 2H), 6.09 (s, 2H), 4.45 (s, 2H), 3.69 (s, 3H), 3.40 (s, 3H), 2.39 (s, 3H).	546.25

[1545]

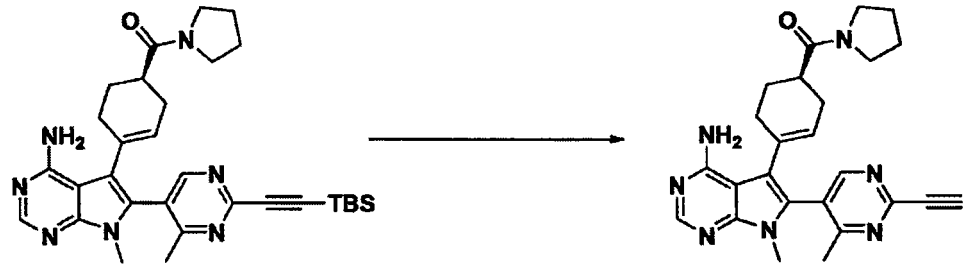
化合物	结构	质子 NMR	MS [M+1]
5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(4-甲氧基-6-(3-甲氧基丙-1-炔-1-基)吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.29 (s, 1H), 7.40 (s, 1H), 7.34 - 7.28 (m, 2H), 7.19 (d, J = 5.1 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 4.39 (s, 2H), 3.87 (s, 3H), 3.61 (s, 3H), 3.37 (s, 3H), 2.41 (d, J = 1.9 Hz, 7H).	525.25

[1546] 实例24

[1547] 流程21

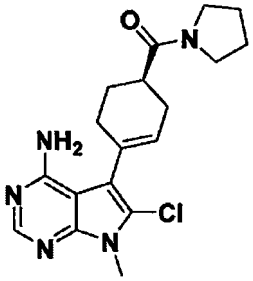
[1548] 

1 2



3

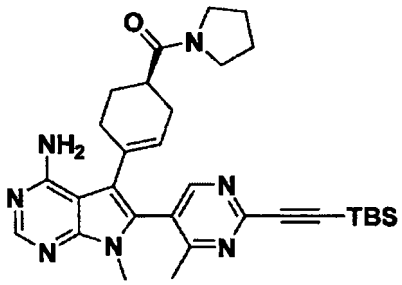
[1549] (1R)-4-{4-氨基-6-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}环己-3-烯-1-甲酸

[1550] 

[1551] 步骤1:向圆底烧瓶中装入(1R)-4-{4-氨基-6-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}环己-3-烯-1-甲酸(1g,3.25mmol)、二甲基甲酰胺(15mL)、吡咯烷(462mg,6.50mmol)、HATU(2.47g,6.50mmol)、NaHCO3(546mg,6.50mmol)及搅拌棒,且在25℃下搅拌溶液1小时。反应混合物用水(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇40:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的(1R)-4-{4-氨基-6-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}环己-3-烯-1-甲酸(1g,85%)。

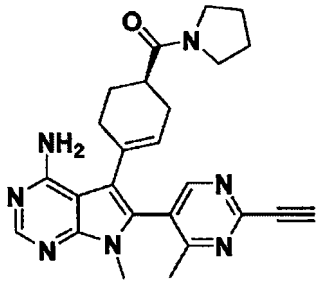
[1552] 6-{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}-7-甲基-5-[(4R)-

4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺

[1553] 

[1554] 步骤2:向可再密封的反应瓶中装入6-氯-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,1.38mmol)、2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)嘧啶(541mg,1.51mmol)、Na2CO3(438mg,4.14mmol)、X-phos(131mg,276μmol)、X-phos G3(116mg,138μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷/H2O(10mL),且在90℃下搅拌混合物1小时。反应混合物用水(30mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇40:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的6-{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,59%)。

[1555] 6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺

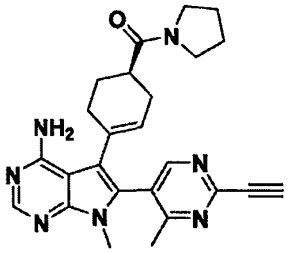
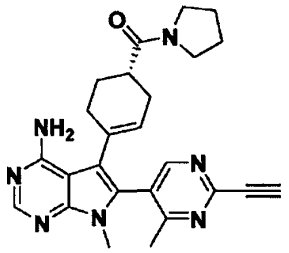
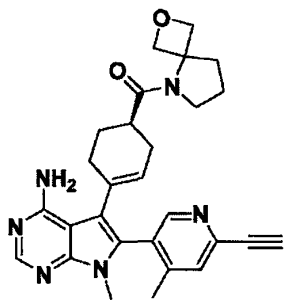
[1556] 

[1557] 步骤3:向圆底烧瓶中装入6-{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(600mg,1.07mmol)、TBAF(1.28mL,1.28mmol)及搅拌棒。添加四氢呋喃(10mL),且在25℃下搅拌溶液1小时。反应混合物用水(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化。冻干产生呈灰白色无定形固体状的6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(109mg,23%)。

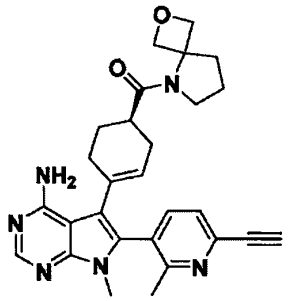
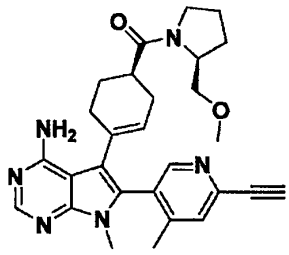
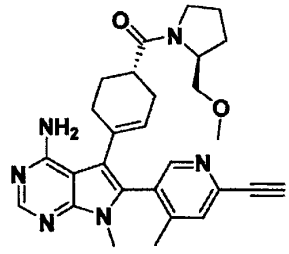
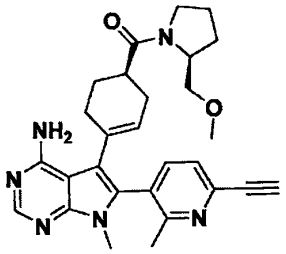
[1558] 根据实例24的方法制备的其它化合物描绘于下表23中。

[1559] 表23.其它示例性化合物

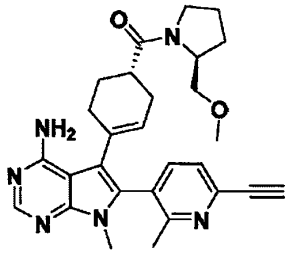
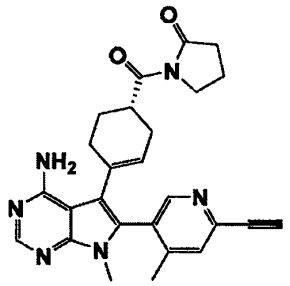
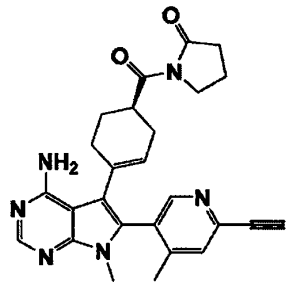
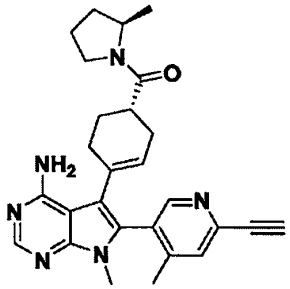
[1560]

化合物	结构	质子 NMR	MS [M+1]
(R)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, J = 13.6 Hz, 1H), 8.14 (s, 1H), 6.65 (s, 2H), 5.67 (s, 1H), 4.51 (d, J = 0.8 Hz, 1H), 3.54 - 3.39 (m, 5H), 3.27 (tt, J = 8.3, 4.3 Hz, 2H), 2.82 - 2.73 (m, 1H), 2.33 (d, J = 1.0 Hz, 3H), 2.19 (s, 2H), 1.96 (s, 2H), 1.80 (dp, J = 27.0, 7.0 Hz, 4H), 1.63 (d, J = 6.5 Hz, 2H).	442.35
(S)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, J = 13.8 Hz, 1H), 8.14 (s, 1H), 6.66 (s, 2H), 5.70 (d, J = 19.4 Hz, 1H), 4.51 (d, J = 0.8 Hz, 1H), 3.58 - 3.39 (m, 5H), 3.26 (dd, J = 6.8, 3.2 Hz, 2H), 2.78 (t, J = 5.9 Hz, 1H), 2.33 (d, J = 1.0 Hz, 3H), 2.20 (s, 2H), 1.97 (s, 2H), 1.85 (q, J = 6.5 Hz, 2H), 1.77 (q, J = 6.6 Hz, 2H), 1.63 (d, J = 6.4 Hz, 2H).	442.15
(R)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(2-氧杂-5-氮杂螺[3.4]辛-5-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.38 (d, J = 7.1 Hz, 1H), 8.12 (d, J = 1.1 Hz, 1H), 7.61 (s, 1H), 6.52 (s, 2H), 5.68 (d, J = 24.1 Hz, 1H), 5.26 (dt, J = 15.3, 4.2 Hz, 2H), 4.41 (d, J = 1.2 Hz, 1H), 4.15 (d, J = 4.9 Hz, 2H), 3.53-3.34 (m, 3H), 3.30-3.25(m, 3H),2.32-2.07 (m, 7H), 1.74-1.49 (m, 5H), 1.22 (s, 1H).	483.15

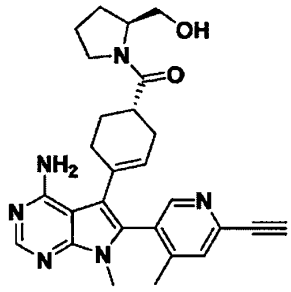
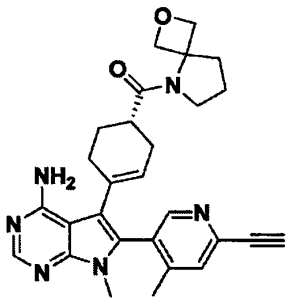
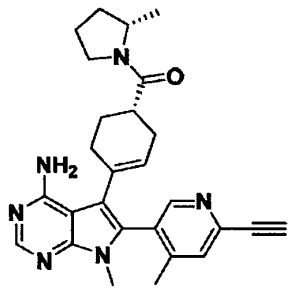
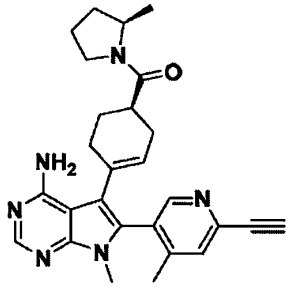
[1561]

化合物	结构	质子 NMR	MS [M+1]
(R)-(4-(4-氨基-6-(6-乙炔基-2-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(2-氧杂-5-氮杂螺[3.4]辛-5-基)甲酮		H NMR (400 MHz, 甲醇-d_4) 8.16 (s, 1H), 7.78 (dd, J = 9.0, 7.9 Hz, 1H), 7.55 (dd, J = 7.9, 4.8 Hz, 1H), 5.88 (d, J = 14.9 Hz, 1H), 5.52-5.44 (m, 2H), 4.41 (dd, J = 5.3, 2.1 Hz, 2H), 3.89 (d, J = 0.9 Hz, 1H), 3.58 (f, J = 14.1, 7.1, 6.6, 3.0 Hz, 2H), 3.48 (s, 3H), 2.90 (d, J = 5.9 Hz, 1H), 2.43 (d, J = 18.4 Hz, 1H), 2.37 (s, 3H), 2.43-2.23 (m, 3H), 2.22 (dd, J = 45.1, 24.5 Hz, 2H), 1.94-1.67 (m, 4H).	483.20
((R)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-(甲氧基甲基)吡咯烷-1-基)甲酮		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 - 8.32 (m, 1H), 8.10 (d, J = 3.4 Hz, 1H), 7.60 (s, 1H), 6.63 (s, 2H), 5.72 (s, 1H), 4.40 (s, 1H), 4.04 (s, 1H), 3.51 - 3.32 (m, 5H), 3.24 - 3.14 (m, 5H), 2.76 (s, 1H), 2.21 (s, 1H), 2.12 (d, J = 4.3 Hz, 3H), 1.82 (d, J = 28.6 Hz, 6H), 1.57 (s, 2H).	485.40
((S)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-(甲氧基甲基)吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.40 (s, 1H), 8.14 (d, J = 3.8 Hz, 1H), 7.63 (s, 1H), 6.52 (s, 1H), 5.65 (d, J = 7.1 Hz, 1H), 4.43 (s, 1H), 4.10 (d, J = 37.6 Hz, 1H), 3.45 (m, J = 11.4, 4.6 Hz, 2H),3.44- 3.35 (m, 3H), 3.23 (d, J = 4.3 Hz, 5H), 2.70 (d, J = 15.0 Hz, 1H), 2.15 (d, J = 13.9 Hz, 5H), 1.93 (d, J = 23.9 Hz, 2H), 1.80 (s, 4H), 1.58 (s, 2H),	485.25
((R)-4-(4-氨基-6-(6-乙炔基-2-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-(甲氧基甲基)吡咯烷-1-基)甲酮		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 - 8.06 (m, 1H), 7.78 - 7.63 (m, 1H), 7.49 (dd, J = 8.0, 3.8 Hz, 1H), 6.58 (d, J = 30.8 Hz, 1H), 5.67 (d, J = 14.1 Hz, 1H), 4.43 - 4.37 (m, 1H), 4.03 (s, 1H), 3.35 (d, J = 1.2 Hz, 5H), 3.24 - 3.12 (m, 5H), 2.76 (s, 1H), 2.25 (d, J = 2.5 Hz, 3H), 2.11 (s, 1H), 1.81 (d, J = 21.3 Hz, 6H), 1.57 (s, 2H).	485.40

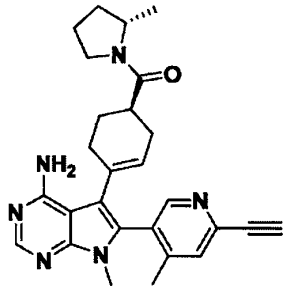
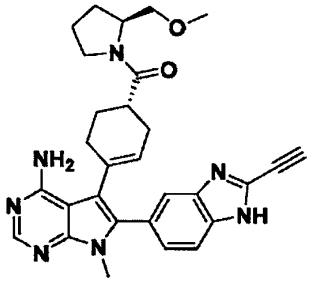
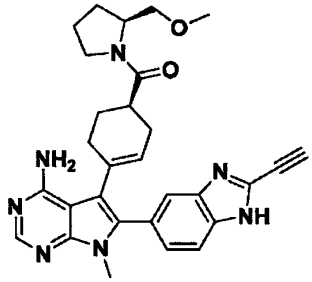
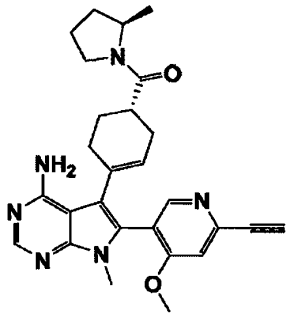
[1562]

化合物	结构	质子 NMR	MS [M+1]
((S)-4-(4-氨基-6-(6-乙炔基-2-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-(甲氧基甲基)吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.14 (d, J = 3.7 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 6.51 (s, 2H), 5.66 (d, J = 12.7 Hz, 1H), 4.43 (s, 1H), 4.08 (d, J = 37.6 Hz, 1H), 3.44 (m, J = 11.4, 4.6 Hz, 2H), 3.38 (d, J = 3.2 Hz, 3H), 3.23 (d, J = 4.9 Hz, 5H), 2.71 (t, J = 10.2 Hz, 1H), 2.28 (d, J = 3.2 Hz, 3H), 2.17 (s, 2H), 1.91 (d, J = 22.3 Hz, 3H), 1.80 (s, J = 7.7, 6.8 Hz,3H), 1.58 (s, 2H).	485.20
(S)-1-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 11.4 Hz, 1H), 8.14 (s, 1H), 7.63 (d, J = 2.4 Hz, 1H), 6.46 (s, 2H), 5.72 (d, J = 24.8 Hz, 1H), 4.43 (s, 1H), 3.65 (m, J = 33.4 Hz, 3H), 3.37 (d, J = 2.7 Hz, 3H), 2.60 - 2.53 (m, 1H), 2.39 - 2.19 (m, 2H), 2.14 (s, 3H), 1.99 - 1.86 (m, 4H), 1.81 - 1.57 (m, 3H).	455.30
(R)-1-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-酮		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (d, J = 8.3 Hz, 1H), 8.12 (s, 1H), 7.64 - 7.57 (m, 1H), 6.43 (s, 2H), 5.70 (d, J = 18.3 Hz, 1H), 4.39 (s, 1H), 3.73 - 3.55 (m, 3H), 3.35 (d, J = 1.9 Hz, 3H), 2.57 - 2.48 (m, 1H), 2.28 (d, J = 23.1 Hz, 2H), 2.11 (s, 3H), 1.89 (p, J = 7.6 Hz, 4H), 1.79 - 1.42 (m, 3H).	455.20
((S)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 - 8.31 (m, 1H), 8.14 (d, J = 3.3 Hz, 1H), 7.63 (s, 1H), 6.54 (s, 2H), 5.67 (d, J = 26.6 Hz, 1H), 4.43 (s, 1H), 4.00 (s, 1H), 3.51 (s, 1H), 3.38 (d, J = 2.7 Hz, 1H), 3.37 (s, 3H), 2.68 (t, J = 1.9 Hz, 1H), 2.53 (s, 1H), 2.14 (d, J = 4.4 Hz, 4H), 2.07 - 1.44 (m, 8H), 1.07 (d, J = 6.2 Hz, 3H).	455.25

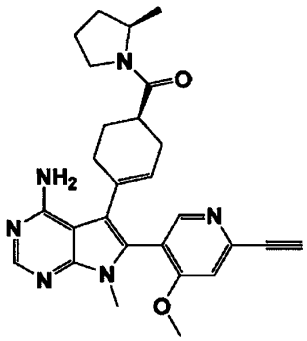
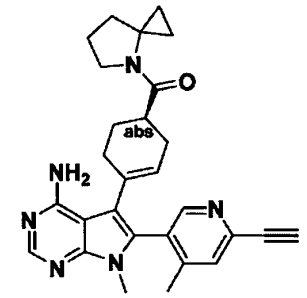
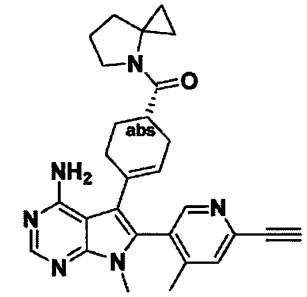
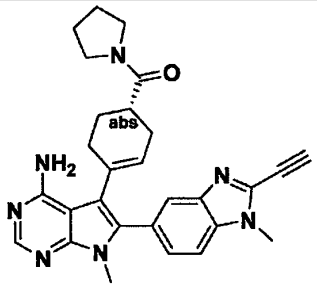
[1563]

化合物	结构	质子 NMR	MS [M+1]
((S)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-(羟基甲基)吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 - 8.36 (m, 1H), 8.14 (d, J = 2.7 Hz, 1H), 7.63 (s, 1H), 6.51 (s, 2H), 5.67 (d, J = 25.9 Hz, 1H), 4.95 - 4.67 (m, 1H), 4.42 (s, 1H), 3.95 (d, J = 15.4 Hz, 1H), 3.47 (dt, J = 10.0, 4.4 Hz, 2H), 3.37 (s, 3H), 3.29 - 3.19 (m, 1H), 2.70 (s, 1H), 2.14 (d, J = 5.2 Hz, 5H), 1.97 - 1.78 (m, 6H), 1.58 (s, 2H).	471.35
(S)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(2-氧杂-5-氮杂螺[3.4]辛-5-基)甲酮		1H NMR: 1H NMR (400 MHz, DMSO-d6) 8.41 (d, J = 8.2 Hz, 1H), 8.15 (s, 1H), 7.71 - 7.56 (m, 1H), 6.59 (s, 1H), 5.71 (d, J = 24.5 Hz, 1H), 5.36 - 5.21 (m, 2H), 4.43 (s, 1H), 4.18 (d, J = 4.9 Hz, 2H), 3.53 - 3.41 (m, 2H), 3.38 (s, 3H), 2.77 (s, 1H), 2.39 - 2.18 (m, 4H), 2.14 (d, J = 2.8 Hz, 3H), 1.94 (d, J = 18.5 Hz, 2H), 1.71 (t, J = 6.8 Hz, 2H), 1.61 (s, 2H).	483.20
6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-[(4S)-4-[(2S)-2-甲基吡咯烷-1-羰基]环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 - 8.24 (m, 1H), 8.10 (d, J = 3.2 Hz, 1H), 7.60 (s, 1H), 5.67 (d, J = 27.0 Hz, 1H), 4.40 (s, 1H), 3.99 (s, 1H),3.44 (s, 2H), 3.35(s, 3H), 2.48 (s, 2H), 2.11 (d, J = 3.6 Hz, 2H), 1.88 (s, 5H), 1.77 - 1.57(m, 4H), 1.19-0.81 (m, 4H).	455.20
((R)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) 8.45-8.37 (m, 1H), 8.13 (d, J = 4.3 Hz, 1H), 7.63 (s, 1H), 6.55 (s, 1H), 5.70 (d, J = 37.1 Hz, 1H), 4.42 (d, J = 2.0 Hz, 1H), 4.01 (s, 1H), 3.47 (t, J = 6.4 Hz, 1H), 3.40-3.35 (m, 4H), 2.72 (d, J = 33.0 Hz, 1H), 2.24 (s, 1H), 2.19-2.13 (m, 4H), 1.85 (d, J = 44.5 Hz, 5H), 1.57 (s, 2H), 1.47 (s, 1H), 1.13-1.03 (m, 3H).	455.20

[1564]

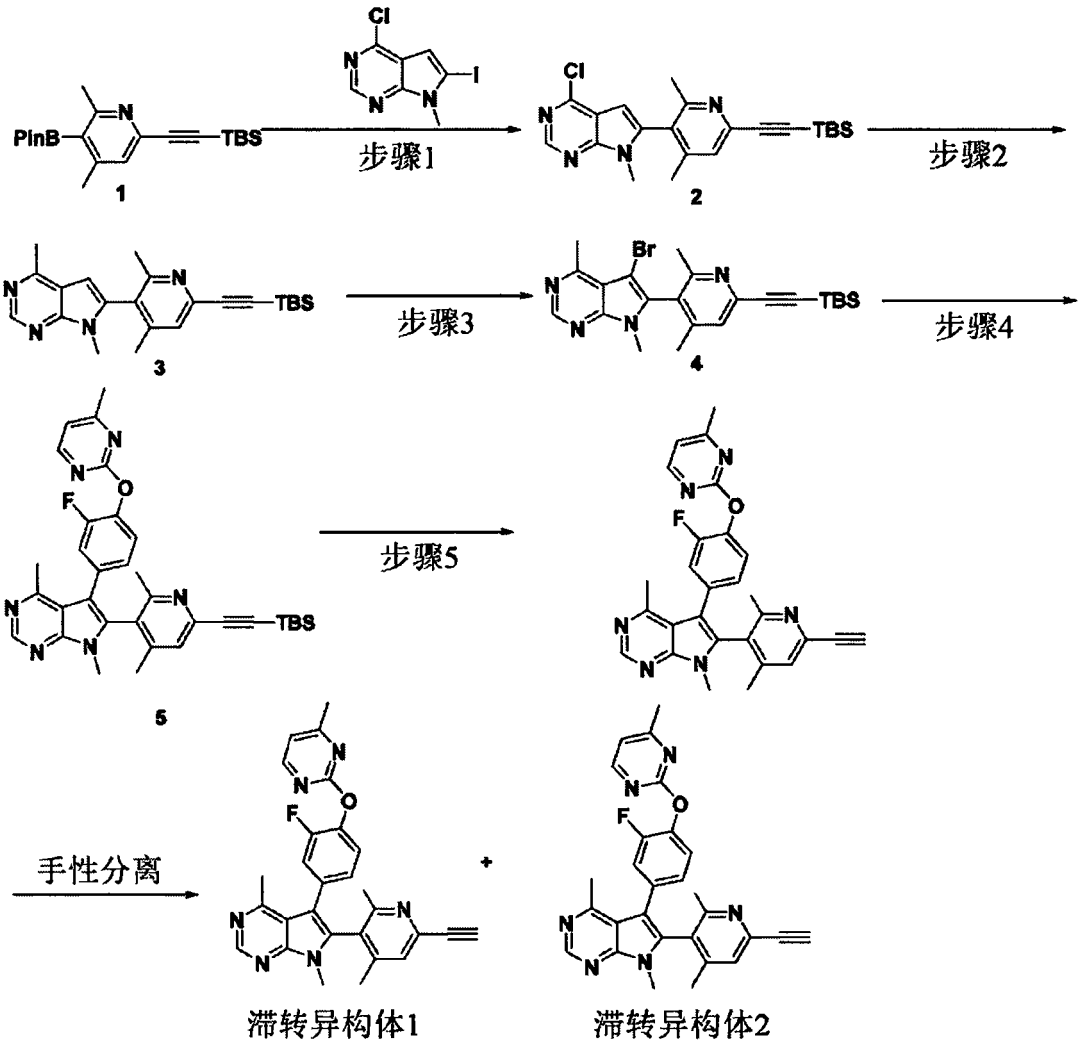
化合物	结构	质子 NMR	MS [M+1]
((R)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-甲基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d6) 8.42-8.37 (m, 1H), 8.14 (d, J = 3.2 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 6.54 (s, 1H), 5.67 (d, J = 26.1 Hz, 1H), 4.42 (s, 1H), 4.05 (d, J = 39.4 Hz, 1H), 3.57 (d, J = 42.9 Hz, 1H), 3.35-3.48 (m, 4H), 2.69 (d, J = 6.9 Hz, 1H), 2.14 (d, J = 4.3 Hz, 5H), 1.94 (d, J = 18.5 Hz, 3H), 1.82 (s, 2H), 1.57 (s, 2H), 1.49 (d, J = 5.7 Hz, 1H), 1.09 (dd, J = 12.6, 6.6 Hz, 3H).	455.15
((S)-4-(4-氨基-6-(2-乙炔基-1H-苯并[d]咪唑-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-(甲氧基甲基)吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 13.32 (s, 1H), 8.12 (d, J = 3.9 Hz, 1H), 7.73 (s, 1H), 7.56 (s, 1H), 7.38 (s, 1H), 6.3(s,2H), 5.79 (s, 1H), 4.71 (s, 1H), 4.02 (s, 1H), 3.59 (s, 3H), 3.53 - 3.37 (m, 3H), 3.24 (s, 4H), 2.72 (s, J = 32.8 Hz, 1H), 2.29 (d, J = 36.4 Hz, 2H), 1.90 (d, J = 13.4 Hz, 3H), 1.80 (d, J = 5.1 Hz, 3H), 1.54 (s, 2H).	510.30
((R)-4-(4-氨基-6-(2-乙炔基-1H-苯并[d]咪唑-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((S)-2-(甲氧基甲基)吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 13.33 (d, J = 10.2 Hz, 1H), 8.13 - 8.08 (m, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.38 (dd, J = 14.6, 8.7 Hz, 1H), 6.59 (s, 2H), 5.80 (s, 1H), 4.72 (d, J = 1.1 Hz, 1H), 4.05 (s,1H), 3.59 (d, J = 6.7 Hz, 3H), 3.49 (d, J = 8.1 Hz, 1H), 3.27 - 3.22 (m, 1H), 3.17 (d, J = 1.3 Hz, 2H), 2.83 (s, 3H), 2.4(s,1H), 2.20 (s, 1H), 1.87 - 1.83 (m, 1H), 1.78 (s, 6H), 1.54 (s, 2H).	510.30
((S)-4-(4-氨基-6-(6-乙炔基-4-甲氧基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ8.28-8.25 (m, 1H), 8.16-8.10 (m, 1H), 7.41 (d, J = 4.3 Hz, 1H), 6.54 (s, 2H), 5.66 (d, J = 33.7 Hz, 1H),4.46 (s, 1H), 4.15-3.96 (m, 1H), 3.91 (d, J = 3.4 Hz, 3H), 3.42 (d, J = 3.4 Hz, 4H), 3.34 (s, 1H), 2.72(s, 1H), 2.17 (s, 2H), 2.04-1.72 (m, 5H), 1.66 (d, J = 30.2 Hz, 2H), 1.50 (d, J = 6.2 Hz, 1H), 1.13- 1.04 (m, 3H).	471.35

[1565]

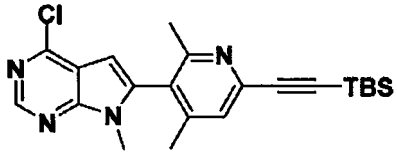
化合物	结构	质子 NMR	MS [M+1]
((R)-4-(4-氨基-6-(6-乙炔基-4-甲氧基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ8.26 (s, 1H), 8.16-8.06 (m, 1H), 7.41 (s, 1H), 6.59 (d, J = 95.2 Hz, 2H), 5.83-5.57 (m, 1H), 4.45 (d, J = 2.5 Hz, 1H), 4.03 (d, J = 8.5 Hz, 2H), 3.91 (s, 3H), 3.48 (s, 1H), 3.42 (d, J = 3.1 Hz, 3H), 2.84-2.65 (m, 1H), 2.36-2.04 (m, 2H), 2.02-1.72 (m,5H), 1.56 (d, J = 60.9 Hz, 3H), 1.17-1.01 (m, 3H).	471.35
(R)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(4-氮杂螺[2.4]庚-4-基)甲酮		^{1}H NMR (400 MHz, DMSO-d6) 8.39 (d, J = 6.1 Hz, 1H), 8.13 (s, 1H), 7.62 (s, 1H), 6.53 (s, 1H), 5.66 (d, J = 28.0 Hz, 1H), 4.42 (s, 1H), 3.77 -3.52 (m, 2H),3.32(m,3H), 2.70 (s, 1H), 2.36 -2.03 (m, 5H), 1.97 -1.51 (m, 8H), 1.36(s,2H),0.39 (s, 2H).	467.25
(S)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(4-氮杂螺[2.4]庚-4-基)甲酮		^{1}H NMR (400 MHz, DMSO-d6) 8.39 (d, J = 6.1 Hz, 1H), 8.13 (s, 1H), 7.62 (s, 1H), 6.53 (s, 1H), 5.66 (d, J = 28.0 Hz, 1H), 4.42 (s, 1H), 3.77 -3.52 (m, 2H),3.32(m,3H), 2.70 (s, 1H), 2.36 -2.04 (m, 5H), 1.98 -1.50 (m, 8H), 1.35(s,2H),0.39 (s, 2H).	467.25
(S)-(4-(4-氨基-6-(2-乙炔基-1-甲基-1H-苯并[d]咪唑-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d6) 8.11 (s, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.47 (dd, J = 8.5, 1.6 Hz, 1H), 6.56 (s, 1H), 5.80 (s, 1H), 5.00 (s, 1H), 3.93 (s, 3H), 3.58 (s, 3H), 3.49 (dt, J = 10.1, 6.6 Hz, 1H), 3.43 -3.37 (m, 1H), 3.28 (d, J = 6.4 Hz, 0H), 3.23 (dd, J = 11.9, 6.6 Hz, 1H), 2.80 (t, J = 5.9 Hz, 1H), 2.26 (q, J = 20.5, 18.0 Hz, 2H), 1.84 (q, J = 6.6 Hz, 4H), 1.55 (s, 2H).	480.25

[1566] 实例25

[1567] 流程22

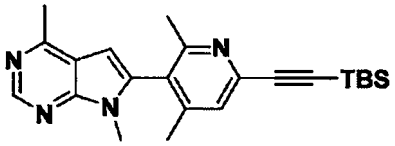
[1568] 

[1569] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶

[1570] 

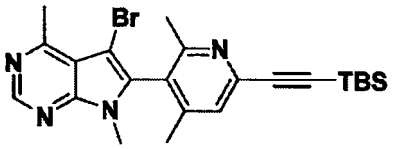
[1571] 步骤1:向可再密封的反应瓶中装入4-氯-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶(1.2g,4.1mmol)、N6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基-3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(1.82g,4.91mmol)、PAd2nBu Pd-G2(0.27g,0.41mmol)、PAd2nBu(0.29g,0.82mmol)、K3PO4(2.61g,12.3mmol)、二恶烷(30mL)、H2O(3mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在70℃下搅拌混合物15小时。真空浓缩反应混合物。所得粗物质通过硅胶色谱(用MeOH/DCM=1/100~1/20洗脱)纯化。真空浓缩,产生呈棕色固体状的6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶(0.7g,42%)。

[1572] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[1573] 

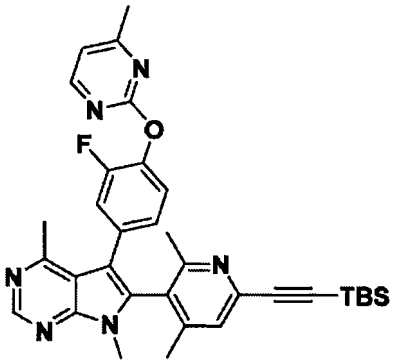
[1574] 步骤2:向可再密封的反应瓶中装入6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶(0.7g,1.7mmol)、Pd(PPh3)4(0.2g,0.17mmol)、THF(20mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加Zn(CH3)2(1M,2.04mL,2.04mmol)。在70℃下搅拌混合物2小时。反应混合物用水淬灭,用DCM萃取,经Na2SO4干燥,真空浓缩。所得粗物质通过硅胶色谱(用MeOH/DCM=1/100~1/30)洗脱)纯化。真空浓缩,产生呈棕色固体状的6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(0.4g,60%)。

[1575] 5-溴-6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[1576] 

[1577] 步骤3:向圆底烧瓶中装入6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(0.4g,1mmol)、DMF(10mL)及搅拌棒。添加NBS(0.18g,1mmol)。搅拌混合物1小时。反应物用饱和$NaHSO_3$水溶液淬灭,用DCM(50mL*3)萃取,合并有机相且用盐水洗涤两次,经Na_2SO_4干燥,真空蒸发,残余物用ACN(25mL)溶解且过滤,滤饼用ACN洗涤,在减压下干燥,得到呈黄色固体状的5-溴-6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(440mg,94%)。

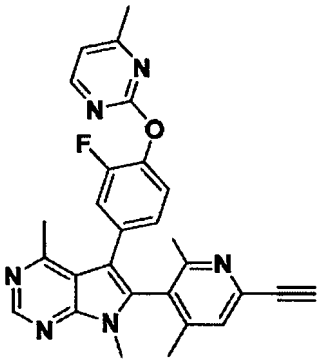
[1578] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[1579] 

[1580] 步骤4:向圆底烧瓶中装入5-溴-6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(440mg,0.94mmol)、2-(2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基)-4-甲基嘧啶(371.5mg,1.1mmol)、Pd(PPh3)4(104mg,0.09mmol)、K3PO4(598mg,2.82mmol)、DME/H2O(10:1,10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物2小时。冷却后,混合物用水稀释,用DCM萃取,经Na_2SO_4干燥,真空蒸发,残余物通过硅胶色谱(用MeOH/DCM=1/100~1/10洗脱)纯化,得到呈棕色固体状的6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(300mg,

54%)。

[1581] 6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

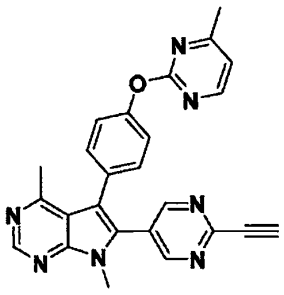
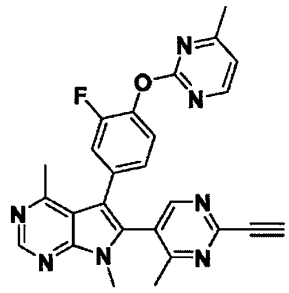
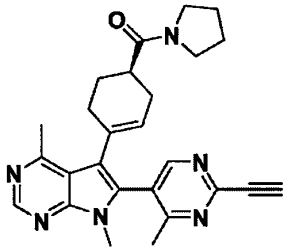
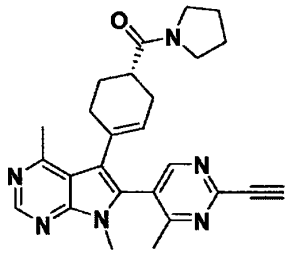
[1582] 

[1583] 步骤5:向圆底烧瓶中装入6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(300mg,0.51mmol)、THF(10mL)及搅拌棒。逐滴添加TBAF(0.61mL,0.61mmol)。在室温下搅拌混合物0.5小时。混合物用水稀释,用DCM萃取,用盐水洗涤,经Na_2SO_4干燥,真空蒸发,残余物通过制备型HPLC纯化,得到白色固体(100mg,41%)。将100mg靶标送交手性分离(柱:CHIRALPAK IF,2*25cm,5um;移动相A:Hex(0.5%2M NH3-MeOH),移动相B:EtOH:DCM=1:1--HPLC;流量:20mL/min;梯度:20B至20B,历时15.5分钟;220/254nm;RT1:10.826;RT2:12.649;注射体积:0.8ml;操作次数:5)。冻干得到前峰(43.4mg)及后峰(40.2mg)。

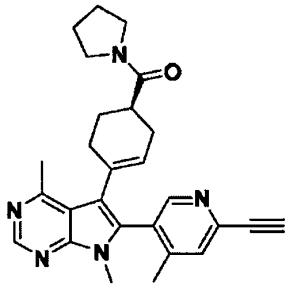
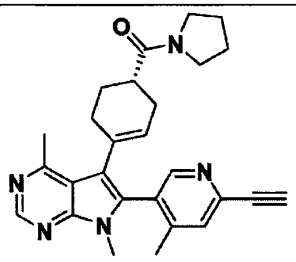
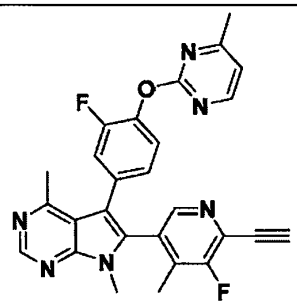
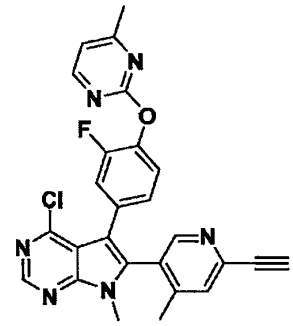
[1584] 根据实例25的方法制备的其它化合物描绘于下表24中。

[1585] 表24.其它示例性化合物

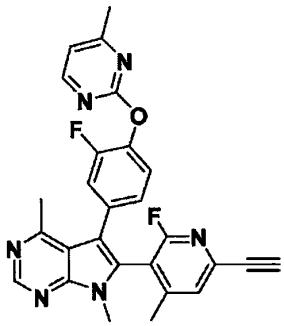
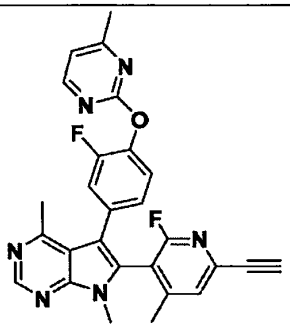
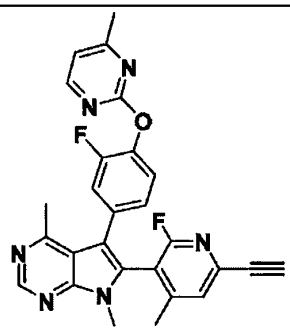
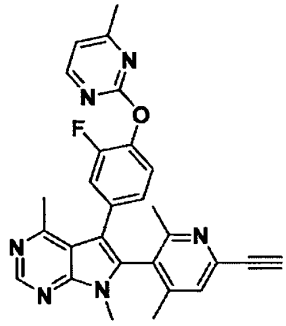
[1586]

化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基嘧啶-5-基)-4,7-二甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 2H), 8.79 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.43-7.35 (m, 2H), 7.25-7.14 (m, 3H), 4.55 (s, 1H), 3.81 (s, 3H), 2.42 (s, 3H), 2.38 (s, 3H).	434.15
6-(2-乙炔基-4-甲基嘧啶-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, J = 17.9 Hz, 2H), 8.49 (d, J = 5.0 Hz, 1H), 7.46 - 7.29 (m, 2H), 7.17 (dd, J = 18.9, 6.7 Hz, 2H), 4.52 (s, 1H), 3.64 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H).	466.25
5-{4,7-二甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-6-基}-2-乙炔基-4-甲基嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 11.1 Hz, 2H), 5.85 - 5.20 (m, 1H), 4.53 (s, 1H), 3.53 (d, J = 1.3 Hz, 3H), 3.45 (td, J = 6.8, 2.9 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.67 (s, 3H), 2.33 (d, J = 3.2 Hz, 4H), 2.22 - 2.00 (m, 4H), 1.99 - 1.81 (m, 2H), 1.77 (q, J = 6.7 Hz, 3H), 1.49 (t, J = 11.9 Hz, 1H).	441.35
5-{4,7-二甲基-5-[(4S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-6-基}-2-乙炔基-4-甲基嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 11.0 Hz, 2H), 5.91 - 5.36 (m, 1H), 4.53 (s, 1H), 3.52 (d, J = 1.3 Hz, 3H), 3.45 (td, J = 6.7, 3.0 Hz, 2H), 3.26 (d, J = 6.9 Hz, 2H), 2.67 (s, 3H), 2.33 (t, J = 2.8 Hz, 4H), 2.15 (d, J = 30.9 Hz, 4H), 1.95 - 1.70 (m, 5H), 1.50 (s, 1H).	441.35

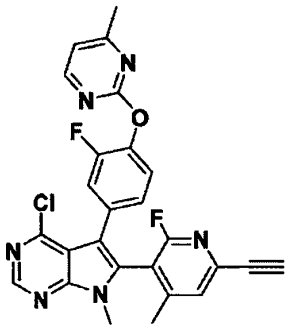
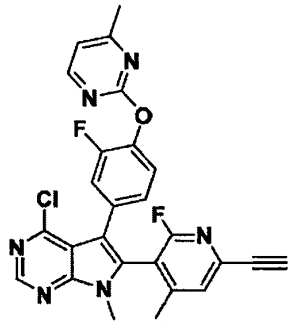
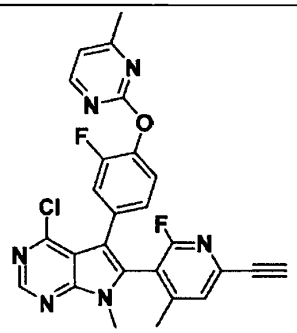
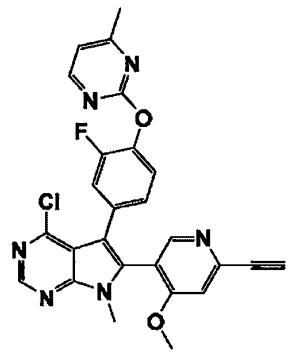
[1587]

化合物	结构	质子 NMR	MS [M+1]
((R)-4-(6-(6-乙炔基-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯基)(吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) 8.69 (s, 1H), 8.44 (d, J = 11.8 Hz, 1H), 7.66 (s, 1H), 5.67 (d, J = 24.4 Hz, 1H), 4.45 (s, 1H), 3.45 (d, J = 11.5 Hz, 5H), 3.26 (t, J = 6.9 Hz, 2H), 2.67 (s, 3H), 2.47 (s, 1H), 2.26-2.02 (m, 7H), 1.92-1.81 (m, 2H), 1.77-1.75 (m, J = 6.7 Hz, 3H), 1.46-1.44 (m, 1H).	440.30
((S)-4-(6-(6-乙炔基-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯基)(吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) 8.69 (s, 1H), 8.44 (d, J = 11.9 Hz, 1H), 7.66 (s, 1H), 5.67 (d, J = 24.4 Hz, 1H), 4.45 (s, 1H), 3.45 (d, J = 11.4 Hz, 5H), 3.26 (t, J = 7.0 Hz, 2H), 2.67 (s, 3H), 2.50 (s, 1H), 2.26-1.99 (m, 7H), 1.94-1.80 (m, 2H), 1.80-1.69 (m, 3H), 1.46-1.44 (m, 1H).	440.25
2-{4-[6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]-2-氟苯氧基}-4-甲基嘧啶		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.49-8.40 (m, 2H), 7.39-7.24 (m, 2H), 7.20-7.06 (m, 2H), 4.80 (d, J = 0.9 Hz, 1H), 3.59 (s, 3H), 2.39 (d, J = 13.1 Hz, 6H), 2.00 (d, J = 2.2 Hz, 3H).	483.30
4-氯-6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶		1H NMR (400 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.58 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 7.60 (s, 1H), 7.34 - 7.26 (m, 2H), 7.18 (d, J = 5.0 Hz, 1H), 7.10 (dt, J = 8.4, 1.4 Hz, 1H), 4.47 (s, 1H), 3.61 (s, 3H), 2.40 (s, 3H), 2.05 (s, 3H).	485.10

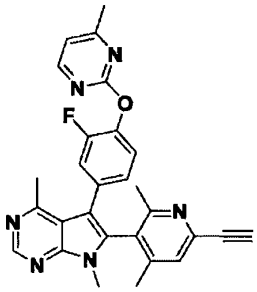
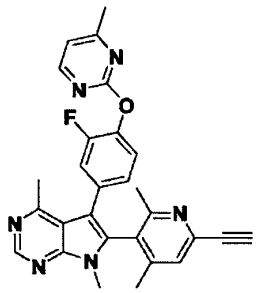
[1588]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		1H NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.62 (s, 1H), 7.37 - 7.29 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 4.61 (s, 1H), 3.61 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H), 2.09 (s, 3H).	483.20
6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶 **滞转异构体 1**		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.62 (s, 1H), 7.37 - 7.29 (m, 2H), 7.19 (d, J = 5.1 Hz, 1H), 7.11 - 7.06 (m, 1H), 4.62 (s, 1H), 3.61 (s, 3H), 2.45 (s, 3H), 2.40 (d, J = 5.3 Hz, 3H), 2.09 (s, 3H).	483.25
6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶 **滞转异构体 2**		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.62 (s, 1H), 7.37 - 7.30 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.11 - 7.06 (m, 1H), 4.62 (s, 1H), 3.61 (s, 3H), 2.46 (s, 3H), 2.41 (s, 3H), 2.09 (s, 3H).	483.25
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 7.45 (s, 1H), 7.34-7.25 (m, 2H), 7.18 (d, J = 5.0 Hz, 1H), 7.07 (d, J = 8.9 Hz, 1H), 4.39 (s, 1H), 3.51 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H), 2.05 (s, 3H).	479.35

[1589]

化合物	结构	质子 NMR	MS [M+1]
4-氯-6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶		1H NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H), 7.63 (s, 1H), 7.31 (t, J = 8.5 Hz, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 4.62 (s, 1H), 3.66 (s, 3H), 2.40 (s, 3H), 2.09 (s, 3H).	503.15
4-氯-6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶 滞转异构体 1		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.63 (s, 1H), 7.36 - 7.29 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.07 - 7.04 (m, 1H), 4.64 (s, 1H), 3.66 (s, 3H), 2.41 (s, 3H), 2.09 (s, 3H)	503.25
4-氯-6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶 滞转异构体 2		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.63 (s, 1H), 7.34 - 7.29 (m, 2H), 7.19 (d, J = 5.1 Hz, 1H), 7.08 - 7.04 (m, 1H), 4.64 (s, 1H), 3.66 (s, 3H), 2.41 (s, 3H), 2.09 (s, 3H).	503.25
2-{4-[4-氯-6-(6-乙炔基-4-甲氧基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]-2-氟苯氧基}-4-甲基嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.31 (s, 1H), 7.44 (s, 1H), 7.34 - 7.25 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.11 - 7.03 (m, 1H), 4.50 (s, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 2.41 (s, 3H).	501.15

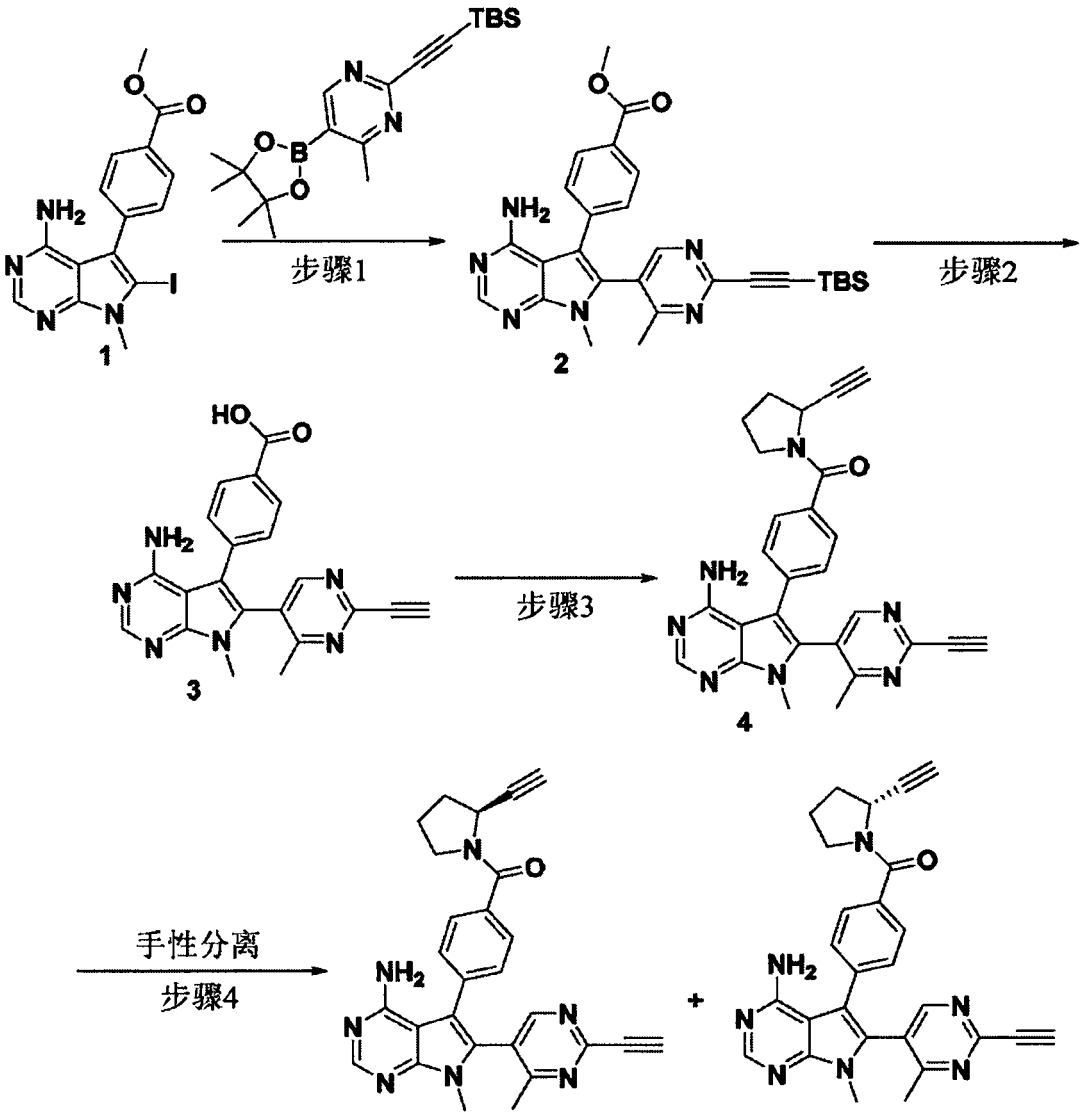
[1590]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶	 滞转异构体 1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H), 7.46 (s, 1H), 7.36 - 7.24 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.11 - 7.04 (m, 1H), 4.40 (s, 1H), 3.53 (s, 3H), 2.46 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H), 2.05 (s, 3H).	479.25
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶	 滞转异构体 2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.24 (m, 2H), 7.18 (d, J = 5.1 Hz, 1H), 7.11 - 7.04 (m, 1H), 4.39 (s, 1H), 3.51 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H), 2.06 (d, J = 14.0 Hz, 3H).	479.25

[1591] 实例26

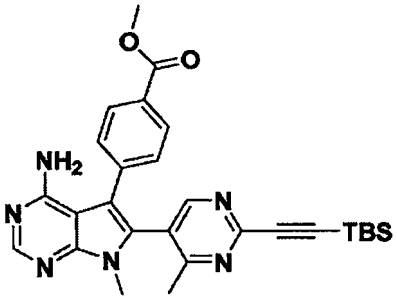
[1592] 流程23

[1593]



[1594] 4-(4-氨基-6-(2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸甲酯

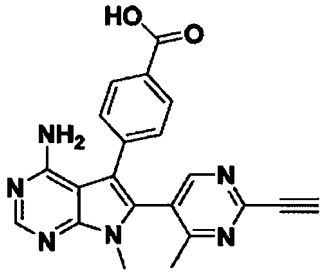
[1595]



[1596] 步骤1:向圆底烧瓶中装入4-(4-氨基-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸甲酯(3g,7.35mmol)、2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)嘧啶(3.26g,8.82mmol)、Pd(dppf)Cl_2(538mg,735μmol)、Cs_2CO_3(4.79g,14.7mmol)、DME:水=10:1(4mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取。有机相经Na2SO4干燥,过滤且真空蒸发。所得粗物质通过硅胶柱色谱来纯化。真空浓缩,产生呈黄色无定形固体状的4-(4-氨基-6-(2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并

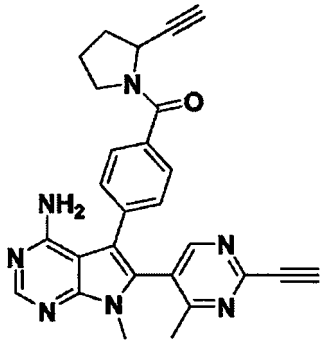
[2,3-d]嘧啶-5-基)苯甲酸甲酯(1.5g,39%)。

[1597] 4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸

[1598] 

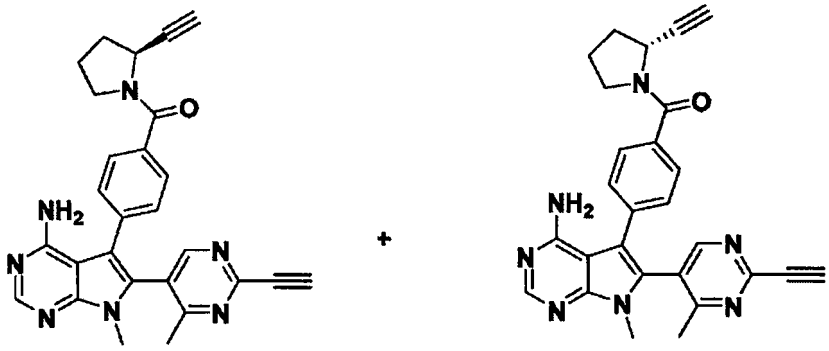
[1599] 步骤2:向圆底烧瓶中装入4-(4-氨基-6-(2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸甲酯(500mg,977μmol)、THF(10mL)及搅拌棒。添加NaOH(2M,1mL,1.95mmol),且在60℃下搅拌溶液1小时。移除溶剂。将混合物溶解于水中且用1M HCl调节至PH=2,且然后用乙酸乙酯萃取。合并有机层且在真空下移除溶剂。由此产生呈黄色无定形固体状的4-(4-氨基--6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯甲酸(230mg,63%)。

[1600] (4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮

[1601] 

[1602] 步骤3:向圆底烧瓶中装入(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮(210mg,0.55mmol)、2-乙炔基吡咯烷(95mg,0.82mmol)、HATU(312mg,0.82mmol)、DIEA(211mg,1.64mmol)、二甲基甲酰胺(5mL)。在室温下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,过滤且真空蒸发。所得粗物质通过制备型HPLC纯化(柱:YMC-Actus Triart C18,30*250,5um;移动相A:水(10MMOL/LNH_4HCO_3),移动相B:ACN;流量:50mL/min;梯度:35B至53B,历时8分钟;220nm;RT1:7.03)。真空浓缩,产生呈灰白色无定形固体状的(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮(60mg,24%)。

[1603] (S)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮及(R)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮

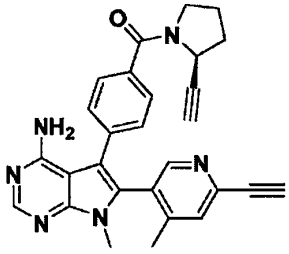
[1604] 

[1605] 步骤4:外消旋(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮(60mg,0.13mmol)通过手性HPLC来纯化(柱:CHIRAL ART纤维素-SB,4.6*100mm,3.0um;移动相:Hex(0.2%IPAmine):(EtOH:DCM=1:1)=50:50)。冻干产生呈灰白色无定形固体状的(S)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮(3.9mg,13%)及(R)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮(13.5mg,45%)。

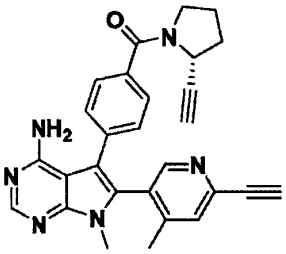
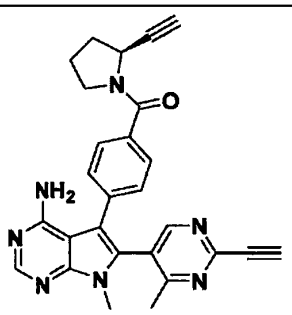
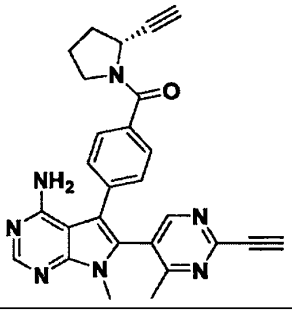
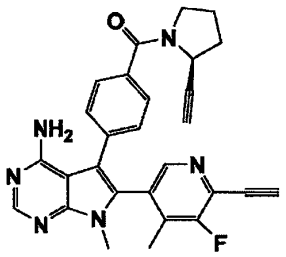
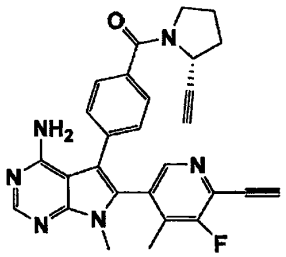
[1606] 根据实例26的方法制备的其它化合物描绘于下表25中。

[1607] 表25.其它示例性化合物

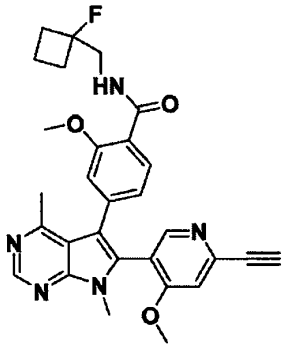
[1608]

化合物	结构	质子 NMR	MS [M+1]
(S)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.24 (s, 1H), 7.53 - 7.42 (m, 3H), 7.22 (d, J = 7.8 Hz, 2H), 6.10 - 6.08 (m, 1H), 4.71 - 4.60 (m, 1H), 4.40 (s, 1H), 3.53 - 3.35 (m, 5H), 3.17 (s, 1H), 2.18 - 2.09 (m, 1H), 2.01 - 1.83 (m, 6H).	461.35

[1609]

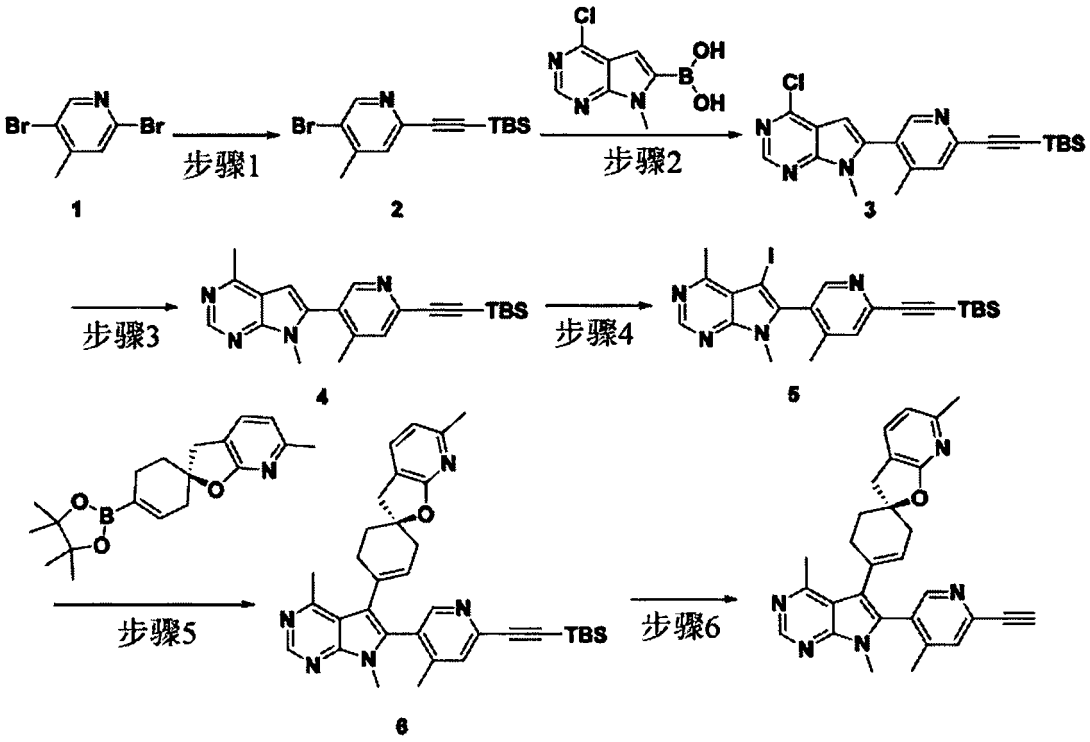
化合物	结构	质子 NMR	MS [M+1]
(R)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.24 (s, 1H), 7.59 - 7.46 (m, 3H), 7.22 (d, J = 7.8 Hz, 2H), 6.09 - 6.07 (m, 1H), 4.72 - 4.60 (m, 1H), 4.39 (s, 1H), 3.53 - 3.48 (m, 5H), 3.17 (s, 1H), 2.19 - 2.11 (m, 1H), 2.01 - 1.81 (m, 6H).	461.35
(S)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.26 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 4.66 (d, J = 50.5 Hz, 1H), 4.48 (d, J = 1.1 Hz, 1H), 3.55 (s, 5H), 3.17 (d, J = 2.0 Hz, 1H), 2.09 (s, 4H), 2.03 - 1.76 (m, 3H).	462.15
(R)-(4-(4-氨基-6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.26 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 4.66 (d, J = 50.5 Hz, 1H), 4.48 (d, J = 1.1 Hz, 1H), 3.55 (s, 5H), 3.17 (d, J = 2.0 Hz, 1H), 2.09 (s, 4H), 2.03 - 1.76 (m, 3H).	462.20
(S)-(4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.25 (s, 1H), 7.51 (d, J = 10.3 Hz, 2H), 7.23 (d, J = 7.7 Hz, 2H), 6.13 (s, 2H), 4.80 (s, 1H), 4.65 (d, J = 49.4 Hz, 1H), 3.51 (s, 5H), 3.17 (s, 1H), 2.43 - 1.67 (m, 7H).	479.35
(R)-(4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(2-乙炔基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.25 (s, 1H), 7.51 (d, J = 7.1 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 6.12 (s, 2H), 4.80 (s, 1H), 4.66 (d, J = 46.9 Hz, 1H), 3.52 (s, 5H), 3.17 (s, 1H), 2.36-1.72 (m, 7H).	479.30

[1610]

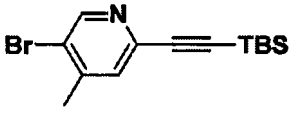
化合物	结构	质子 NMR	MS [M+1]
4-(6-(6-乙炔基-4-甲氧基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-((1-氟环丁基) 甲基)-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.28 (t, J = 6.1 Hz, 1H), 8.20 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.41 (s, 1H), 7.02 (s, 1H), 6.91 (d, J = 7.9 Hz, 1H), 4.45 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.67 (d, J = 6.1 Hz, 1H), 3.62 (s, 1H), 3.60 (s, 3H), 2.40 (s, 3H), 2.23 - 2.14 (m, 4H), 1.76 (dd, J = 11.2, 7.1 Hz, 1H), 1.58 - 1.49 (m, 1H).	514.25

[1611] 实例27

[1612] 流程24

[1613] 

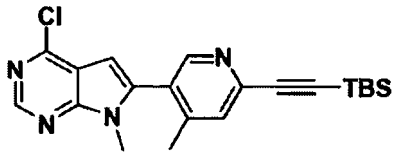
[1614] 5-溴-2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶

[1615] 

[1616] 步骤1:向可再密封的反应瓶中装入2,5-二溴-4-甲基吡啶(3g,11.9mmol)、叔丁基(乙炔基)二甲基硅烷(1.82g,13.0mmol)、TEA(3.60g,35.7mmol)、CuI(452mg,2.38mmol)、二甲基甲酰胺(40mL)及搅拌棒,添加Pd(PPh3)2Cl2(834mg,1.19mmol),随后抽真空且用氮气吹扫三次。在50℃下搅拌混合物2小时。反应混合物用H2O(20mL)稀释,且用EA(120mL)萃取水相三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(300g柱;用PE/EA 50/1-20/1洗脱)。真空浓缩,产生呈黄色无定形固体状的5-溴-2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶(3.10g,83.9%)。

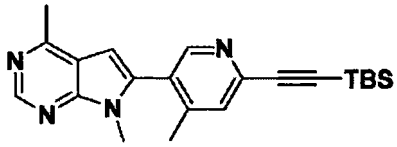
[1617] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-4-氯-7-甲基-7H-吡

咯并[2,3-d]嘧啶

[1618] 

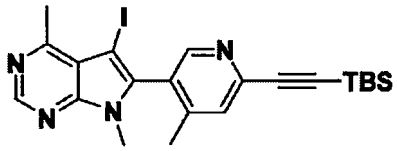
[1619] 步骤2:向可再密封的反应瓶中装入5-溴-2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶(3g,9.66mmol)、{4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}硼酸(2.43g,11.5mmol)、K3PO4(6.12g,28.9mmol)、Pd(dppf)Cl2(706mg,966μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷/H2O(50mL),且在70℃搅拌混合物2小时。水相用二甲基甲酰胺(100mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(300g柱;用PE/EA 10/1洗脱)。真空浓缩,产生呈橙色无定形固体状的2-[2-(叔丁基二甲基硅烷基)乙炔基]-5-{4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-4-甲基吡啶(1.60g,41.7%)。

[1620] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[1621] 

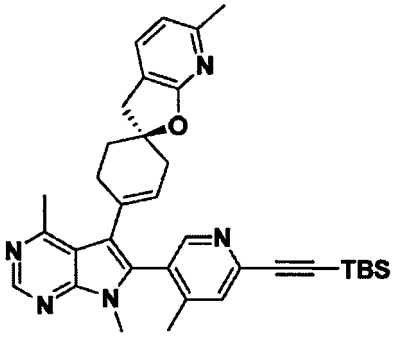
[1622] 步骤3:向可再密封的反应瓶中装入2-[2-(叔丁基二甲基硅烷基)乙炔基]-5-{4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-4-甲基吡啶(1.5g,3.77mmol)、二甲基锌(359mg,3.77mmol)、Pd(PPh3)4(435mg,377μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二甲基甲酰胺(20mL),且在90℃下搅拌混合物1小时。反应混合物用H2O(10mL)稀释,且水相用EA(100mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(300g柱;用二氯甲烷/甲醇40/1洗脱)。真空浓缩,产生呈灰白色无定形固体状的2-[2-(叔丁基二甲基硅烷基)乙炔基]-5-{4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-4-甲基吡啶(1.2g,84.4%)。

[1623] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-5-碘-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[1624] 

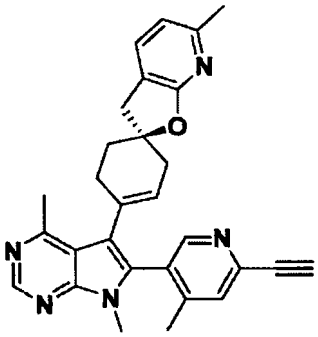
[1625] 步骤4:向圆底烧瓶中装入2-[2-(叔丁基二甲基硅烷基)乙炔基]-5-{4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-4-甲基吡啶(1.1g,2.92mmol)、TFA(849mg,8.76mmol)、DCM(15mL)及搅拌棒。在0℃下添加NIS(722mg,3.21mmol),升温至室温。混合物用饱和NaHSO3水溶液淬灭直至pH至8-9,用DCM(100mL*3)萃取,合并有机相且经Na_2SO_4干燥,真空浓缩,产生呈黄色无定形固体状的2-[2-(叔丁基二甲基硅烷基)乙炔基]-5-{5-碘-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-4-甲基吡啶(1.20g,81.5%)。

[1626] (R)-4-(6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-6′-甲基-3′H-螺[环己烷-1,2′-呋喃并[2,3-b]吡啶]-3-烯

[1627] 

[1628] 步骤5:向可再密封的反应瓶中装入(1R)-6′-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-3′H-螺[环己烷-1,2′-呋喃并[2,3-b]吡啶]-3-烯(40mg,122μmol)、2-[2-(叔丁基二甲基硅烷基)乙炔基]-5-{5-碘-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-4-甲基吡啶(73.3mg,146μmol)、K_3PO_4(25.8mg,122μmol)、Pd(dppf)Cl_2(89.2mg,122μmol)及搅拌棒,随后抽真空且用氮气吹扫。添加DME/H_2O(2mL),且在90℃下搅拌混合物1小时。反应混合物用H_2O(1mL)稀释,且水相用EA(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(10g柱;用二氯甲烷/甲醇15/1洗脱)。真空浓缩,产生呈黑色无定形固体状的(1R)-4-(6-{6-[2-(叔丁基-二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-6′-甲基-3′H-螺[环己烷-1,2′-呋喃并[2,3-b]吡啶]-3-烯(35mg,49.8%)。

[1629] (R)-4-(6-(6-乙炔基-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-6′-甲基-3′H-螺[环己烷-1,2′-呋喃并[2,3-b]吡啶]-3-烯

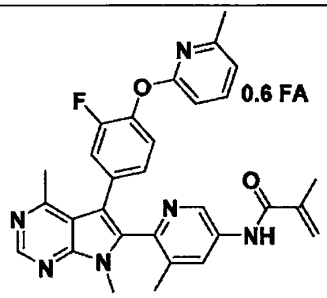
[1630] 

[1631] 步骤6:向圆底烧瓶中装入(1R)-4-(6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-6′-甲基-3′H-螺[环己烷-1,2′-呋喃并[2,3-b]吡啶]-3-烯(30mg,52.0μmol)、氟化铯(23.6mg,156μmol)及搅拌棒。添加THF(2mL),且在50℃下搅拌溶液2小时。过滤且蒸发。所得粗物质通过HPLC纯化(柱:XBridge Shield RP18OBD柱,30*150mm,5um;移动相A:水(10MMOL/L NH_4HCO_3+0.1%$NH_3\cdot H_2O$),移动相B:ACN;流量:60mL/min;梯度:30B至55B,历时7分钟;220nm;RT1:5.97;RT2)。冻干产生呈灰白色无定形固体状的(1R)-4-[6-(6-乙炔基-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]-6′-甲基-3′H-螺[环己烷-1,2′-呋喃并[2,3-b]吡啶]-3-烯(3.90mg,16.9%)。

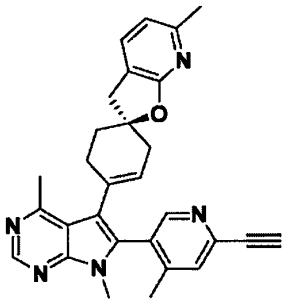
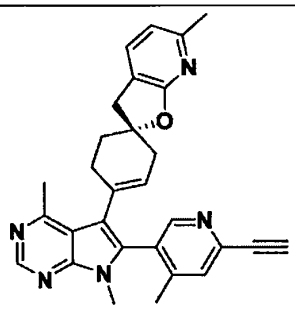
[1632] 根据实例27的方法制备的其它化合物描绘于下表26中。

[1633] 表26.其它示例性化合物

[1634]

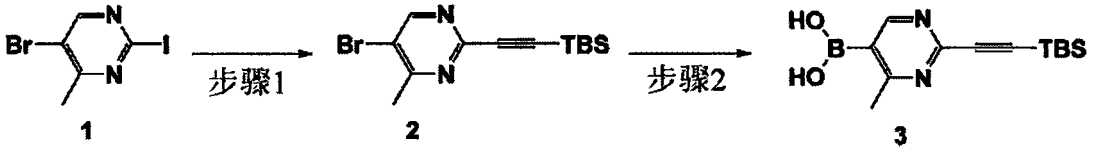
化合物	结构	质子 NMR	MS [M+1]
N-(6-(5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-5-甲基吡啶-3-基)甲基丙烯酰胺；部分甲酸盐		1H NMR (400 MHz, DMSO-d6) δ 10.12 (s, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.78 (s, 1H), 8.23 (d, J = 4.8 Hz, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.75 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 7.68 - 7.63 (m, 1H), 7.27 - 7.16 (m, 2H), 7.02 (dd, J = 12.6, 8.1 Hz, 2H), 6.86 (t, J = 7.4 Hz, 1H), 5.87 (t, J = 1.0 Hz, 1H), 5.60 (d, J = 1.9 Hz, 1H), 3.61 (s, 3H), 3.33 (s, 3H), 2.28 (s, 3H), 1.97 (t, J = 1.2 Hz, 3H), 1.89 (s, 3H).	523.25

[1635]

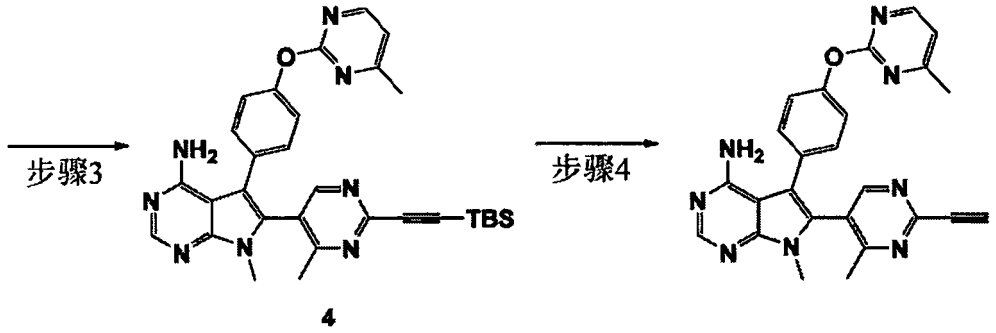
化合物	结构	质子 NMR	MS [M+1]
(1R)-4-[6-(6-乙炔基-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]-6'-甲基-3'H-螺[环己烷-1,2'-呋喃并[2,3-b]吡啶]-3-烯		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.49 (d, J = 6.4 Hz, 1H), 7.69 (d, J = 4.4 Hz, 1H), 7.41 (dd, J = 7.3, 3.3 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 5.60 (d, J = 37.3 Hz, 1H), 4.47 (d, J = 2.1 Hz, 1H), 3.49 (s, 3H), 2.99-2.83 (m, 1H), 2.72 (s, 3H), 2.68 (p, J = 2.2 Hz, 1H), 2.47 - 2.31 (m, 2H), 2.30 (s, 3H), 2.25 (d, J = 18.4 Hz, 1H), 2.17 (d, J = 1.5 Hz, 3H), 2.12 - 1.94 (m, 1H), 1.89 (dd, J = 12.7, 6.2 Hz, 1H), 1.74 (dq, J = 14.0, 6.4 Hz, 1H).	462.30
(S)-4-(6-(6-乙炔基-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-6'-甲基-3'H-螺[环己烷-1,2'-呋喃并[2,3-b]吡啶]-3-烯		1H NMR (400 MHz, DMSO-d6) δ8.71 (s, 1H), 8.49 (d, J = 6.4 Hz, 1H), 7.69 (d, J = 4.3 Hz, 1H), 7.41 (dd, J = 7.2, 3.4 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 5.65 (s, 1H), 4.47 (d, J = 2.1 Hz, 1H), 3.52 - 3.47 (m, 3H), 2.91 (dd, J = 29.8, 16.2 Hz, 1H), 2.72 (s, 3H), 2.38 (d, J = 16.3 Hz, 3H), 2.30 (s, 3H), 2.27 (s, 1H), 2.19 - 2.14 (m, 3H), 2.06 (s, 1H), 1.89 (dd, J = 12.5, 6.1 Hz, 1H), 1.74 (dq, J = 14.1, 6.4 Hz, 1H).	462.20

[1636] 实例28

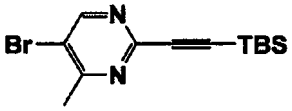
[1637] 流程25



[1638]

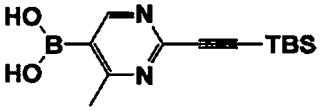


[1639] 5-溴-2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶

[1640] 

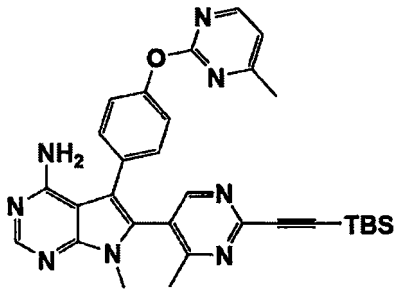
[1641] 步骤1:向可再密封的反应瓶中装入5-溴-2-碘-4-甲基嘧啶(600mg,2.00mmol)、CuI(152mg,800μmol)、Et_3N(606mg,6.00mmol)、$Pd(PPh_3)_2Cl_2$(280mg,400μmol)、DMF(15mL)及搅拌棒,随后抽真空且用氮气吹扫三次,添加叔丁基(乙炔基)二甲基硅烷(280mg,2.00mmol),且在50℃下搅拌混合物2小时。反应混合物用水(20mL)稀释,且水相用乙酸乙酯(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过TLC(PE:EA=8:1)来纯化。真空浓缩,产生呈灰白色无定形固体状的5-溴-2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶(500mg,80%)。

[1642] (2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基嘧啶-5-基)硼酸

[1643] 

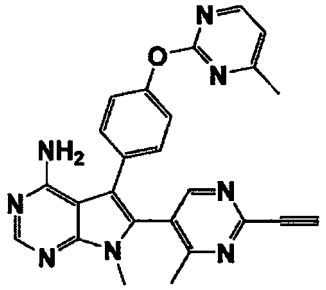
[1644] 步骤2:向可再密封的反应瓶中装入5-溴-2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶(480mg,1.54mmol)、4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,3,2-二氧杂硼杂环戊烷(467mg,1.84mmol)、AcOK(452mg,4.62mmol)、$Pd(dppf)Cl_2$(112mg,154μmol),添加二恶烷(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次,且在80℃下搅拌混合物2小时。反应混合物用水(15mL)稀释,且水相用EA(15mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(乙腈/水0%~60%,30分钟)。冻干产生呈灰白色无定形固体状的{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}硼酸(400mg,94%)。

[1645] 6-(2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基嘧啶-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1646] 

[1647] 步骤3:向可再密封的反应瓶中装入6-碘-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(520mg,1.13mmol)、{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}硼酸(380mg,1.37mmol)、Na_2CO_3(358mg,3.38mmol)、Pd(dppf)Cl_2(82.6mg,113μmol),添加DMF/H2O=16/1(15mL)及搅拌棒,随后抽真空且用氮气吹扫三次,且在90℃下搅拌混合物1小时。反应混合物用水(15mL)稀释,且水相用DCM(15mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(DCM/MeOH=15/1)。冻干产生呈黄色无定形固体状的6-{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(200mg,34%)。

[1648] 6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

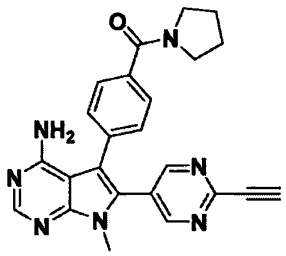
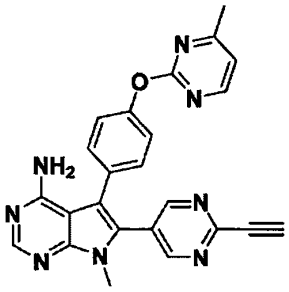
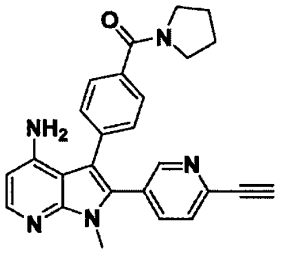
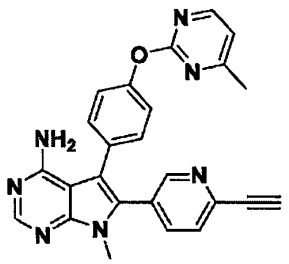
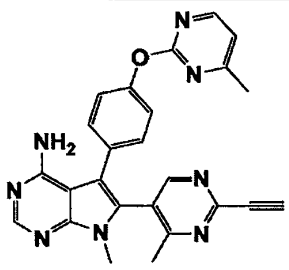
[1649] 

[1650] 步骤4:向圆底烧瓶中装入6-{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(180mg,319μmol)、TBAF(638μg,638μmol)及搅拌棒。添加四氢呋喃(5mL),且在25℃下搅拌溶液1小时。反应混合物用水(10mL)稀释,且水相用二氯甲烷(10mL)萃取三次。合并的有机层用盐水洗涤十次,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(柱:SunFire Prep C18 OBD柱,19×150mm 5um 10nm;移动相:水(0.05%FA),移动相B:CAN(0.1%DEA)--HPLC--;流量:25mL/min;梯度:15B至38B,历时8分钟;220nm;RT1:6.36)。冻干产生呈黄色无定形固体状的6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(31.1mg,21%)。

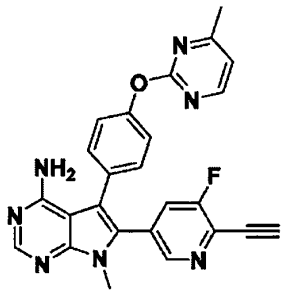
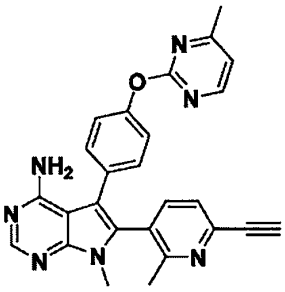
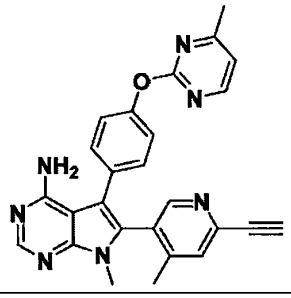
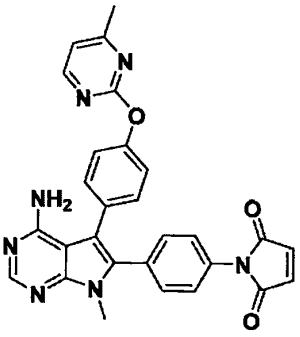
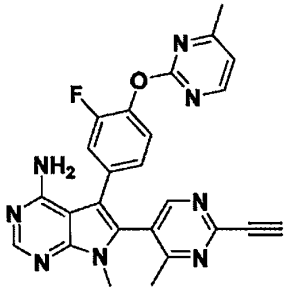
[1651] 根据实例28的方法制备的其它化合物描绘于下表27中。

[1652] 表27.其它示例性化合物

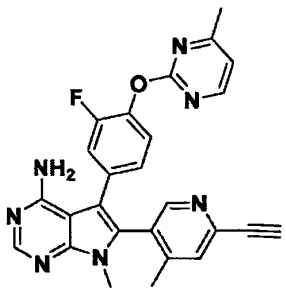
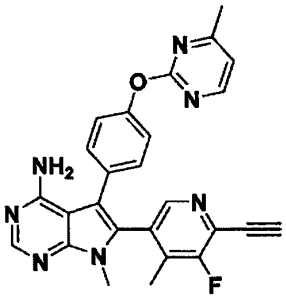
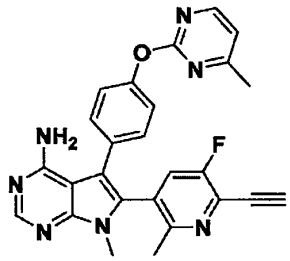
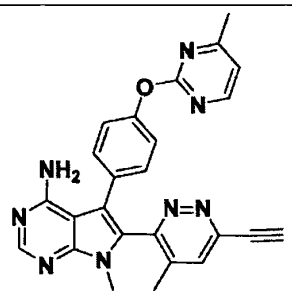
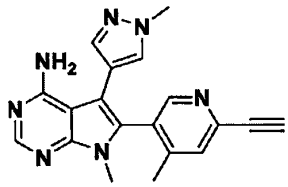
[1653]

化合物	结构	质子 NMR	MS [M+1]
(4-(4-氨基-6-(2-乙炔基嘧啶-5-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 8.75 (s, 2H), 8.25 (s, 1H), 7.60 - 7.43 (m, 2H), 7.38 - 7.21 (m, 2H), 5.81 (s, 1H), 4.52 (s, 1H), 3.72 (s, 3H), 3.45 (dt, J = 17.5, 6.5 Hz, 4H), 1.85 (dq, J = 18.0, 6.8 Hz, 4H).	424.10
6-(2-乙炔基嘧啶-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 2H), 8.48 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.38 - 7.31 (m, 2H), 7.28 - 7.21 (m, 2H), 7.17 (d, J = 5.0 Hz, 1H), 6.08 (s, 1H), 4.52 (s, 1H), 3.72 (s, 3H), 2.42 (s, 3H).	435.20
(4-(4-氨基-2-(6-乙炔基吡啶-3-基)-1-甲基-1H-吡咯并[2,3-b]吡啶-3-基)苯基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 - 8.41 (m, 1H), 8.24 (s, 1H), 7.84 (dd, J = 8.0, 2.3 Hz, 1H), 7.61 (dd, J = 8.1, 0.8 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 4.44 (s, 1H), 3.66 (s, 3H), 3.44 (dt, J = 17.6, 6.4 Hz, 4H), 1.90 - 1.79 (m, 4H).	423.10
6-(6-乙炔基吡啶-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 - 8.45 (m, 2H), 8.23 (s, 1H), 7.89 (dd, J = 8.1, 2.3 Hz, 1H), 7.63 (dd, J = 8.1, 0.9 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.25 - 7.18 (m, 2H), 7.16 (d, J = 5.1 Hz, 1H), 4.44 (s, 1H), 3.66 (s, 3H), 2.42 (s, 3H).	434.10
6-(2-乙炔基-4-甲基嘧啶-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.30 - 7.23 (m, 2H), 7.23 - 7.13 (m, 3H), 6.06 (s, 2H), 4.49 (s, 1H), 3.55 (s, 3H), 2.41 (s, 3H), 2.14 (s, 3H).	449.20

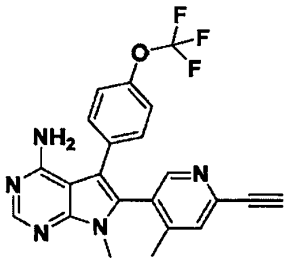
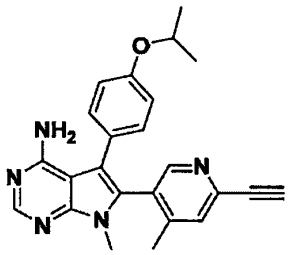
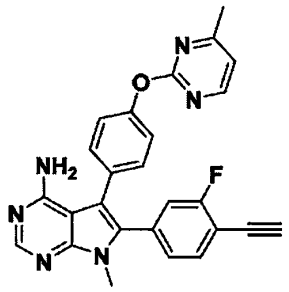
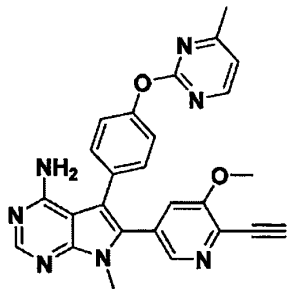
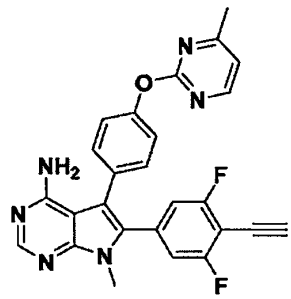
[1654]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-5-氟吡啶-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.31 (t, J = 1.6 Hz, 1H), 8.25 (s, 1H), 8.02 (dd, J = 10.0, 1.8 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.28 - 7.20 (m, 2H), 7.17 (d, J = 5.0 Hz, 1H), 4.84 (d, J = 0.8 Hz, 1H), 3.71 (s, 3H), 2.42 (s, 3H).	452.15
6-(6-乙炔基-2-甲基吡啶-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) 8.46 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.28 -7.21 (m, 2H), 7.21 -7.12 (m, 3H), 6.01 (s, 1H), 4.41 (s, 1H), 3.48 (s, 3H), 2.41 (s, 3H), 2.14 (s, 3H).	448.20
6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 - 8.44 (m, 2H), 8.24 (s, 1H), 7.56 (s, 1H), 7.28 - 7.21 (m, 2H), 7.21 - 7.12 (m, 3H), 4.41 (s, 1H), 3.48 (s, 3H), 2.41 (s, 3H), 2.02 (s, 3H).	448.20
1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-1H-吡咯-2,5-二酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.2 Hz, 1H), 8.25 (s, 1H), 7.55 - 7.51 (m, 2H), 7.50 - 7.40 (m, 2H), 7.33(dd, J = 2.0 Hz, 2H), 7.31 - 7.20(m, 4H), 7.16 (d, J = 4.8 Hz, 1H), 3.65(s, 3H), 2.40(s, 3H).	504.15
6-(2-乙炔基-4-甲基嘧啶-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) 8.81 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.26 -7.16 (m, 2H), 7.08 - 7.01 (m, 1H), 6.19 (s, 2H), 4.49 (s, 1H), 3.54 (s, 3H), 2.41 (s, 3H), 2.15 (s, 3H).	467.20

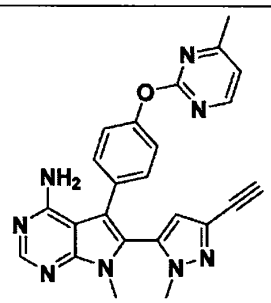
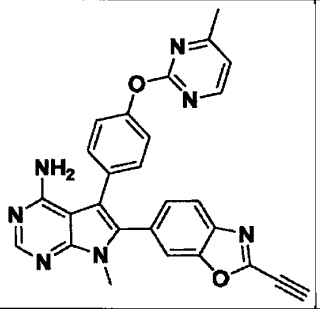
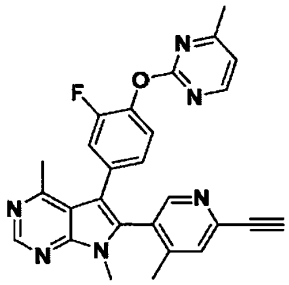
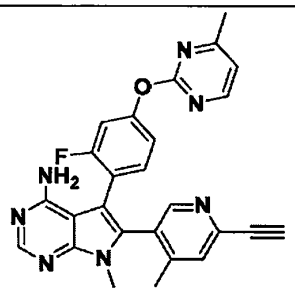
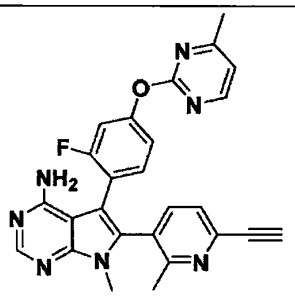
[1655]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51(s, 1H), 8.47 (S, 1H), 8.24 (s, 1H), 7.58(s,1H), 7.36 - 7.30(m, 1H), 7.19 - 7.16 (m, 2H), 7.06 - 7.03 (m, 1H), 4.42 (s, 1H), 3.47 (s, 3H), 2.41 (s, 3H), 2.02 (s, 3H).	466.20
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) 8.47 (d, J = 5.0 Hz, 1H), 8.40 (s, 1H), 8.25 (s, 1H), 7.28 -7.22 (m, 2H), 7.22-7.12 (m, 3H), 4.80 (d, J = 0.8 Hz, 1H), 3.52 (s, 3H), 2.40 (s, 3H), 1.96 (d, J = 2.2 Hz, 3H).	466.25
6-(6-乙炔基-5-氟-2-甲基吡啶-3-基)-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6)8.47(d, J=5.0Hz,1H), 8.25(s,1H), 8.04(d, J = 9.3 Hz,1H), 7.30-7.23 (m,2H), 7.23-7.16 (m,2H), 7.15(d, J = 5.0Hz, 1H), 4.80(d, J=0.8Hz, 1H), 3.52 (s, 3H), 2.41(s,3H), 2.08(d, J =1.1Hz, 3H).	466.20
6-(6-乙炔基-4-甲基哒嗪-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.27 (s, 1H), 7.39 - 7.29 (m, 3H), 7.28 - 7.20 (m, 2H), 7.17 (d, J = 5.0 Hz, 1H), 6.08 (s, 2H), 4.97 (s, 1H), 3.83 (s, 3H), 2.42 (s, 3H), 2.28 (d, J = 0.9 Hz, 3H).	449.20
6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-(1-甲基-1H-吡唑-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6)8.43 (s, 1H),8.19(s, 1H),7.62(d, J = 0.7 Hz,1H), 7.57(s,1H), 7.17(d, J = 0.8 Hz,1H),6.16(s, 1H),4.41(s,1H),3.79(s,3H),3.43(s,3H),2.02(s,3H).	344.15

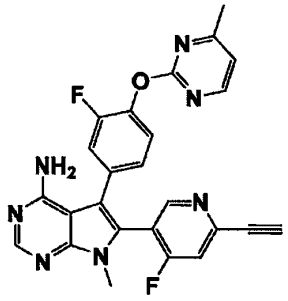
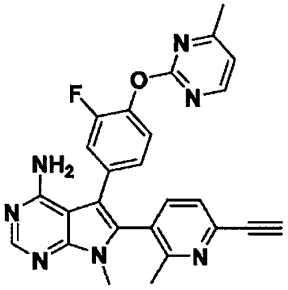
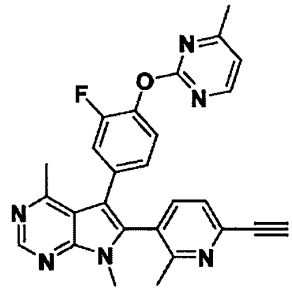
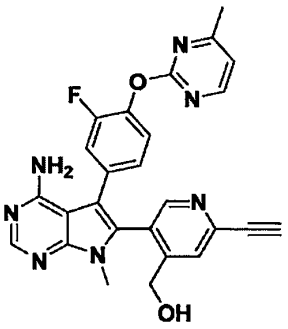
[1656]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-[4-(三氟甲氧基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR: 1H NMR (400 MHz, DMSO-d6) δ 8.46 (s, 1H), 8.24 (s, 1H), 7.55 (s, 1H), 7.31 (q, J = 8.7 Hz, 4H), 6.05 (s, 1H), 4.41 (s, 1H), 3.47 (s, 3H), 1.97 (s, 3H).	424.10
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(4-异丙氧基苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.21 (s, 1H), 7.53 (s, 1H), 7.12-7.04 (m, 2H), 6.91-6.84 (m, 2H), 5.95 (s, 2H), 4.58 (hept, J = 6.0 Hz, 1H), 4.39 (s, 1H), 3.46 (s, 3H), 1.98 (s, 3H), 1.25 (d, J = 6.0 Hz, 6H).	398.30
6-(4-乙炔基-3-氟苯基)-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, 氯仿-d) δ 8.40 (d, J = 5.6 Hz, 2H), 7.32 (s, 1H), 7.29 (s, 2H), 7.25 - 7.20 (m, 2H), 7.05 (d, J = 1.6 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.95 (d, J = 5.0 Hz, 1H), 5.13 (s, 2H), 3.77 (s, 3H), 3.39 (s, 1H), 2.53 (s, 3H).	451.05
6-(6-乙炔基-5-甲氧基吡啶-3-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 8.09 (d, J = 1.7 Hz, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.35 - 7.26 (m, 2H), 7.25 - 7.17 (m, 2H), 7.14 (d, J = 5.0 Hz, 1H), 4.50 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 2.40 (s, 3H).	464.05
6-(4-乙炔基-3,5-二氟苯基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d6) 8.48 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.36-7.30(m,2H), 7.28-7.21(m,4H),7.19-7.13 (m, 1H), 4.91 (s, 1H), 3.69 (s, 3H), 2.41 (s, 3H).	469.15

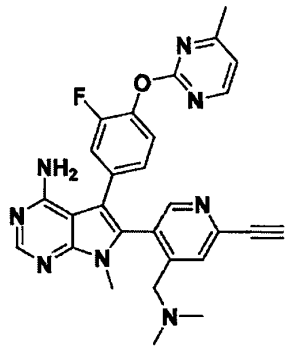
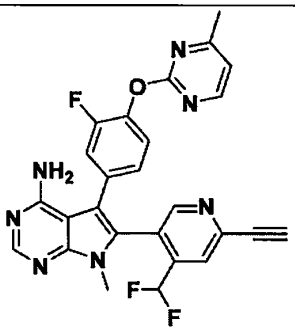
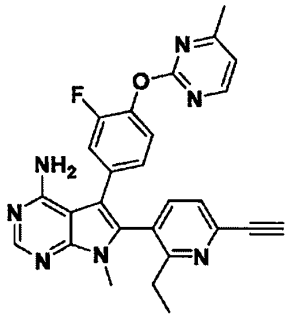
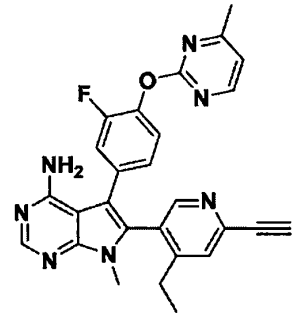
[1657]

化合物	结构	质子 NMR	MS [M+1]
6-(3-乙炔基-1-甲基-1H-吡唑-5-基)-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 7.34-7.20 (m, 4H), 7.16 (d, J = 5.0 Hz, 1H), 6.91 (s, 1H), 4.23 (s, 1H), 3.57 (s, 3H), 3.33 (s, 3H), 2.42 (s, 3H).	437.25
6-(2-乙炔基苯并[d]恶唑-6-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.88-7.80 (m, 2H), 7.44 (dd, J = 8.3, 1.6 Hz, 1H), 7.35-7.27 (m, 2H), 7.20-7.12 (m, 3H), 5.75 (s, 1H), 5.16 (s, 1H), 3.64 (s, 3H), 2.40 (s, 3H).	474.30
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.55 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 7.59 (t, J = 0.9 Hz, 1H), 7.38 - 7.26 (m, 2H), 7.18 (d, J = 5.0 Hz, 1H), 7.16 - 7.09 (m, 1H), 4.44 (s, 1H), 3.56 (s, 3H), 2.41 (d, J = 8.9 Hz, 6H), 2.06 (s, 3H).	465.15
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(2-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 5.0 Hz, 1H), 8.40 (s, 1H), 8.24 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.45 - 7.24 (m, 1H), 7.23 - 7.14 (m, 2H), 7.07 (dd, J = 8.4, 2.3 Hz, 1H), 6.01 (m, 2H), 4.40 (s, 1H), 3.49 (s, 3H), 2.42 (s, 3H), 2.06 (d, J = 19.2 Hz, 3H).	466.20
6-(6-乙炔基-2-甲基吡啶-3-基)-5-(2-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d = 4.8 Hz, 1H), 8.24 (s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.53 - 7.44 (m, 1H), 7.31 (m, 1H), 7.18 (m, 2H), 7.12 - 7.01 (m, 1H), 6.01 (m, 2H), 4.40 (s, 1H), 3.49 (s, 3H), 2.42 (s, 3H), 2.18 (m, 3H).	466.15

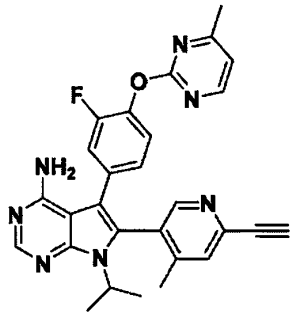
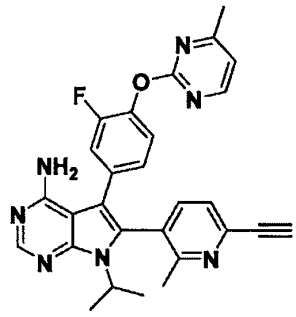
[1658]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-氟吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 10.1 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.76 (d, J = 10.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.27 - 7.23 (m, 1H), 7.23 - 7.17 (m, 1H), 7.10 - 6.99 (m, 1H), 6.17 (s, 1H), 4.63 (s, 1H), 3.63 - 3.56 (m, 3H), 2.42 (s, 3H).	470.10
6-(6-乙炔基-2-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.20 - 7.11 (m, 2H), 7.06 - 6.99 (m, 1H), 6.13 (s, 1H), 4.42 (s, 1H), 4.42 (s, 5H), 3.47 (s, 1H), 2.41 (s, 1H), 2.14 (s, 1H),	466.15
2-{4-[6-(6-乙炔基-2-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]-2-氟苯氧基}-4-甲基嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.37 - 7.27 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 4.44 (s, 1H), 3.57 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H), 2.19 (s, 3H).	465.25
(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)甲醇		1H NMR (400 MHz, DMSO-d6) δ 8.54 (d, J = 0.8 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.67 (s, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.06 (dd, J = 9.3, 1.6 Hz, 1H), 5.48 (t, J = 5.7 Hz, 1H), 4.46 (s, 1H), 4.25 (dd, J = 15.7, 5.8 Hz, 1H), 4.03 (dd, J = 15.6, 5.9 Hz, 1H), 3.46 (s, 3H), 2.41 (s, 3H).	482.15

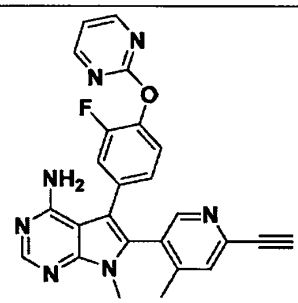
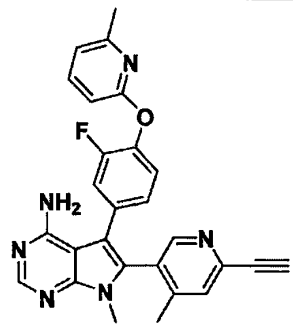
[1659]

化合物	结构	质子 NMR	MS [M+1]
6-(4-((二甲基氨基)甲基)-6-乙炔基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.62 (d, J = 0.8 Hz, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.66 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.19 - 7.13 (m, 2H), 4.46 (s, 1H), 3.46 (s, 3H), 3.23 (d, J = 15.1 Hz, 1H), 2.85 (d, J = 15.2 Hz, 1H), 2.40 (s, 3H), 1.97 (s, 6H).	509.40
6-(4-(二氟甲基)-6-乙炔基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d6) 8.81 (d, J = 0.9 Hz, 1H), 8.44 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.82 (s, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.24 - 7.11 (m, 2H), 7.03 (ddd, J = 8.3, 2.1, 0.9 Hz, 1H), 6.73 (s, 1H), 6.12 (s, 1H), 4.62 (s, 1H), 3.46 (s, 3H), 2.37 (s, 3H).	502.15
6-(2-乙基-6-乙炔基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (300 MHz, DMSO-d6) δ 8.43 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.20 - 7.05 (m, 2H), 6.99 (d, J = 8.2 Hz, 1H), 6.11 (s, 1H), 4.38 (s, 1H), 3.35 (s, 3H), 2.42 - 2.21 (m, 4H), 0.90 (t, J = 7.5 Hz, 3H).	480.15
6-(4-乙基-6-乙炔基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.47 (d, *J* = 5.0 Hz, 1H), 8.24 (s, 1H), 7.58 (s, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.22 - 7.12 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.13 (s, 1H), 4.44 (s, 1H), 3.46 (s, 3H), 2.39 (d, *J* = 10.2 Hz, 4H), 2.22 (dt, *J* = 14.9, 7.6 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H).	480.30

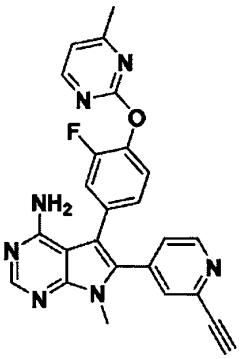
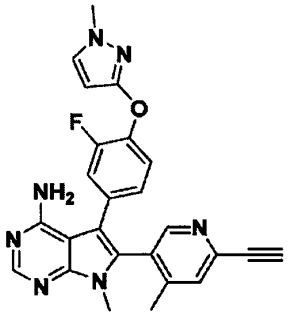
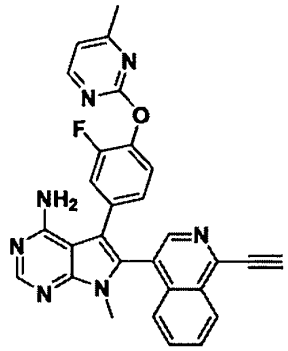
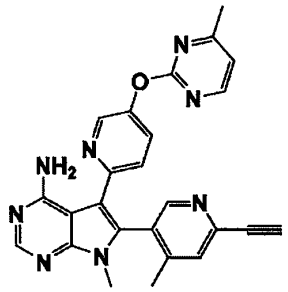
[1660]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (300 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.56 (s, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.22 - 7.11 (m, 2H), 7.03 (d, J = 8.6 Hz, 1H), 6.08 (s, 2H), 4.43 (s, 1H), 4.11 - 4.00 (m, 1H), 2.41 (s, 3H), 2.06 (d, J = 14.2 Hz, 3H), 1.62 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 6.7 Hz, 3H).	494.20
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺	异构体1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.56 (s, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.21 - 7.12 (m, 2H), 7.04 (dd, J = 8.2, 2.1 Hz, 1H), 6.10 (s, 1H), 4.42 (s, 1H), 4.07 (p, J = 6.8 Hz, 1H), 2.41 (s, 3H), 2.04 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 6.8 Hz, 3H).	494.35
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺	异构体2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.56 (s, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.21 - 7.12 (m, 2H), 7.04 (dt, J = 8.3, 1.4 Hz, 1H), 6.09 (s, 1H), 4.42 (s, 1H), 4.07 (p, J = 6.8 Hz, 1H), 2.41 (s, 3H), 2.04 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 6.8 Hz, 3H).	494.35
6-(6-乙炔基-2-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.22 - 7.10 (m, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.10 (s, 1H),4.43 (s, 1H), 4.13 - 4.02 (m, 1H), 2.41 (s, 3H), 2.16 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 6.8 Hz, 3H).	494.20

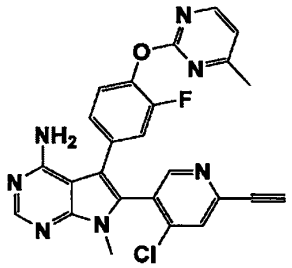
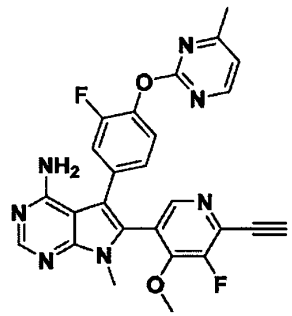
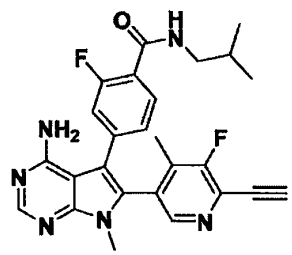
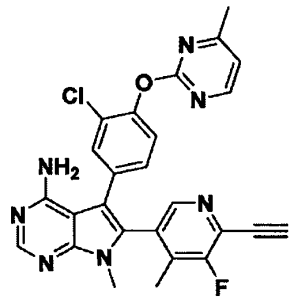
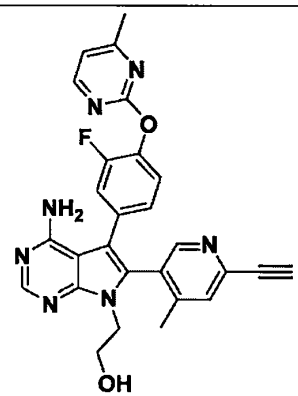
[1661]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-2-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺	异构体1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.52 (dd, J = 7.9, 0.7 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.21 - 7.11 (m, 2H), 7.02 (ddd, J = 8.3, 2.1, 0.9 Hz, 1H), 6.04 (s, 2H), 4.42 (s, 1H), 4.08 (p, J = 6.7 Hz, 1H), 2.41 (s, 3H), 2.16 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 6.8 Hz, 3H).	494.35
6-(6-乙炔基-2-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺	异构体2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.21 - 7.12 (m, 2H), 7.02 (d, J = 8.1 Hz, 1H), 6.04 (s, 1H) 4.42 (s, 1H), 4.08 (t, J = 6.8 Hz, 1H), 2.41 (s, 3H), 2.16 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H), 1.50 (d, J = 6.8 Hz, 3H)	494.35
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-(嘧啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) δ 8.68 (d, J = 4.8 Hz, 2H), 8.52 (s, 1H), 8.27 (d, J = 2.7 Hz, 1H), 7.59 (s, 1H), 7.41 -7.29 (m, 2H), 7.19 - 7.06 (m, J = 8.3 Hz, 2H), 6.15 (s, 1H),4.43 (s, 1H), 3.47 (s, 3H), 2.04 (s, 3H).	452.15
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((6-甲基吡啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d6) δ 8.49 (s, 1H), 8.22 (s, 1H), 7.71 (dd, J = 8.2, 7.3 Hz, 1H), 7.53 (d, J = 0.8 Hz, 1H), 7.22 (t, J = 8.4 Hz, 1H), 7.10 (dd, J = 11.5, 2.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.97 (d, J = 3.4 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.15 (s, 2H), 4.39 (s, 1H), 3.46 (s, 3H), 2.26 (s, 3H), 1.97 (s, 3H).	465.35

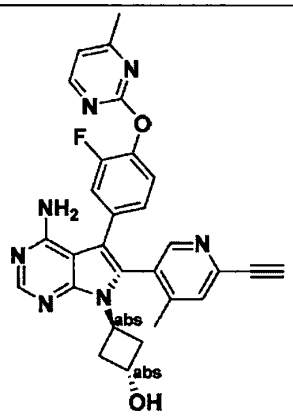
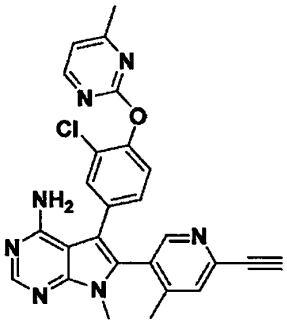
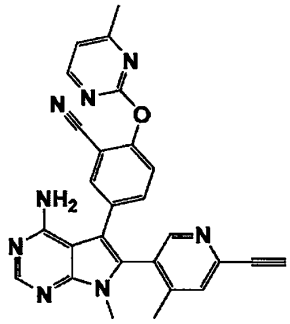
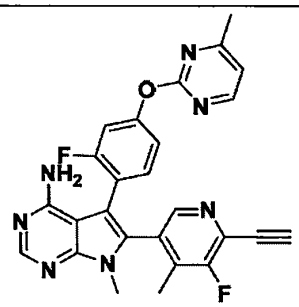
[1662]

化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基吡啶-4-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (300 MHz, DMSO-d6) δ 8.60 (dd, J = 5.2, 0.9 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.53 (t, J = 1.3 Hz, 1H), 7.46 - 6.99 (m, 5H), 4.39 (s, 1H), 3.68 (s, 3H), 2.43 (s, 3H).	452.15
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((1-甲基-1H-吡唑-3-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (300 MHz, DMSO-d6) δ 8.45 (s, 1H), 8.20 (s, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 0.9 Hz, 1H), 7.17 - 7.04 (m, 2H), 6.92 (dt, J = 8.4, 1.5 Hz, 1H), 6.10 (s, 1H), 5.82 (d, J = 2.3 Hz, 1H), 4.39 (s, 1H), 3.70 (s, 3H), 3.43 (s, 3H), 1.97 (s, 3H).	454.10
6-(1-乙炔基异喹啉-4-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.48 - 8.37 (m, 2H), 8.29 (s, 1H), 7.87 - 7.80 (m, 2H), 7.63 - 7.56 (m, 1H), 7.26 - 7.17 (m, 2H), 7.14 (d, J = 5.1 Hz, 1H), 7.05 - 7.01 (m, 1H), 6.15 (s, 1H), 4.97 (s, 1H), 3.43 (s, 3H), 2.36 (s, 3H).	502.20
6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.58 (d, J = 2.7 Hz, 1H), 8.50 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.22 (s, 1H), 7.70 (s, 1H), 7.46 (dd, J = 8.8, 2.8 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 4.58 (s, 1H), 3.55 (s, 3H), 2.48 (s, 3H), 2.17 (s, 3H).	449.30

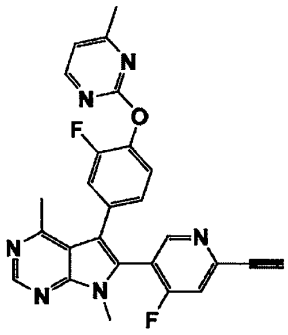
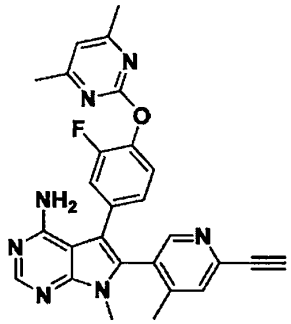
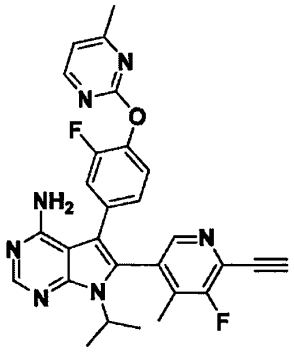
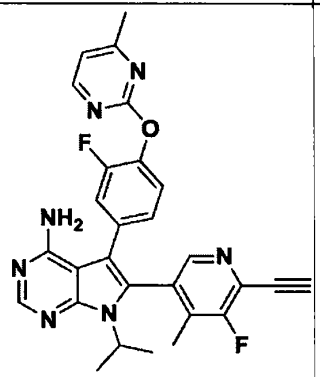
[1663]

化合物	结构	质子 NMR	MS [M+1]
6-(4-氯-6-乙炔基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 7.98 (s, 1H), 7.35 (s, 1H), 7.23 - 7.15 (m, 2H), 7.09 - 6.99 (m, 1H), 6.18 (s, 1H), 4.63 (s, 1H), 3.53 (s, 3H), 2.42 (s, 3H).	486.25
6-(6-乙炔基-5-氟-4-甲氧基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ8.48 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 8.18 (s, 1H), 7.38-7.34 (m, 1H), 7.23-7.18 (m, 2H), 7.08-7.05 (m, 1H), 6.13 (s, 1H), 4.84 (d, J = 1.0 Hz, 1H), 3.91 (d, J = 4.5 Hz, 3H), 3.56 (s, 3H), 2.51 (s, 3H).	500.15
4-(4-氨基-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟-N-异丁基苯甲酰胺		^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.23 (s, 2H), 7.51 (t, J = 7.9 Hz, 1H), 7.10-6.98 (m, 2H), 6.16 (s, 1H), 4.79 (d, J = 0.8 Hz, 1H), 3.48 (s, 3H), 3.09-2.98 (m, 2H), 1.95 (d, J = 2.1 Hz, 3H), 1.79 (dp, J = 13.4, 6.7 Hz, 1H), 0.86 (d, J = 6.7 Hz, 6H).	475.30
5-(3-氯-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.44 (s, 1H), 8.26 (s, 1H), 7.38 (s, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.22 - 7.13 (m, 2H), 6.18 (s, 2H), 4.81 (d, J = 0.8 Hz, 1H), 3.52 (s, 3H), 2.41 (s, 3H), 1.96 (d, J = 2.1 Hz, 3H).	500.15
2-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-7-基)乙-1-醇		^{1}H NMR (300 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.54 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.22 - 7.09 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.14 (s, 1H), 4.79 (t, J = 5.6 Hz, 1H), 4.42 (s, 1H), 4.09 (dd, J = 13.3, 6.5 Hz, 1H), 3.85 (dt, J = 13.5, 6.2 Hz, 1H), 3.52 (q, J = 6.0 Hz, 2H), 2.41 (s, 3H), 1.97 (s, 3H).	496.30

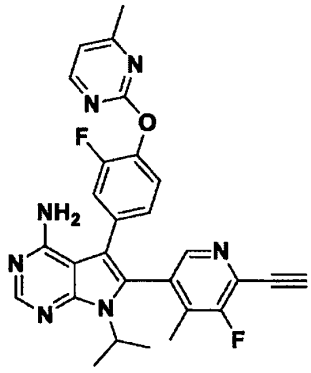
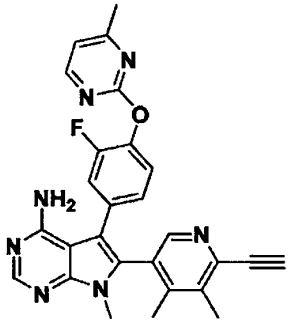
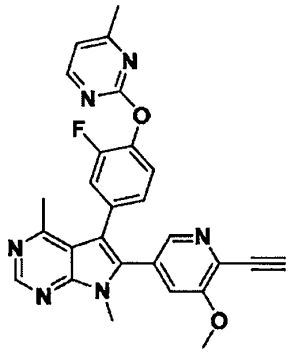
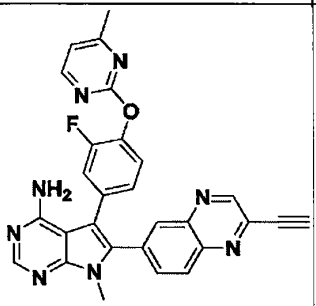
[1664]

化合物	结构	质子 NMR	MS [M+1]
(1S,3r)-3-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-7-基)环丁-1-醇		1H NMR (400 MHz, 氯仿-d) δ 8.44 (s, 1H), 8.41 - 8.33 (m, 2H), 7.42 (s, 1H), 7.28 (s, 2H), 7.23 (t, J = 8.2 Hz, 1H), 7.04 - 6.92 (m, 3H), 6.19 (s, 1H), 5.22 (s, 2H), 4.23 - 4.14 (m, 1H), 4.10 (p, J = 7.4 Hz, 1H), 3.24 (s, 1H), 3.03 (dt, J = 10.6, 6.5 Hz, 4H), 2.51 (s, 3H), 2.04 (s, 3H).	522.20
5-(3-氯-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) δ 8.52 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.58 (s, 1H), 7.41 -7.27 (m, 2H), 7.25 - 7.13 (m, 2H),6.14-6.11(m,1H), 4.43 (s, 1H), 3.47 (s, 3H), 2.42 (s, 3H), 2.02 (s, 3H).	482.15
5-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-((4-甲基嘧啶-2-基)氧基)苯甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 5.1 Hz, 2H), 8.25 (s, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.58 (d, J = 0.8 Hz, 1H), 7.49 (dd, J = 8.6, 2.3 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 5.1 Hz, 1H), 6.21 (s, 2H), 4.43 (s, 1H), 3.47 (s, 3H), 2.44 (s, 3H), 2.01 (s, 3H).	473.20
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-5-{2-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 5.0 Hz, 1H), 8.32 (d, J = 6.6 Hz, 1H), 8.25 (s, 1H), 7.35 (t, J = 8.6 Hz, 1H), 7.26 - 7.16 (m, 2H), 7.12 - 7.02 (m, 1H), 6.08 (s, 1H), 4.79 (d, J = 0.8 Hz, 1H), 3.54 (s, 3H), 2.41 (s, 3H), 2.00 (d, J = 24.8 Hz, 3H).	484.30

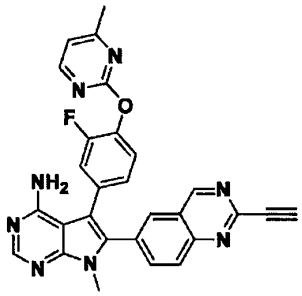
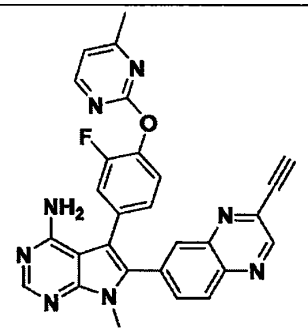
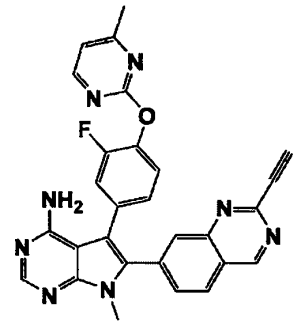
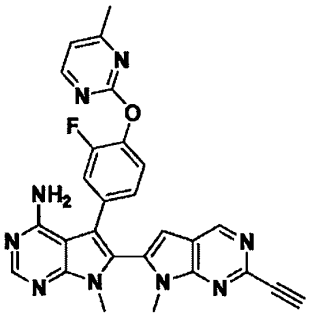
[1665]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-氟吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.65 (d, J = 10.0 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.79 (d, J = 10.0 Hz, 1H), 7.43 - 7.30 (m, 2H), 7.17 (dd, J = 12.6, 6.7 Hz, 2H), 4.64 (s, 1H), 3.70 (s, 3H), 2.41 (d, J = 2.9 Hz, 6H).	469.30
5-{4-[(4,6-二甲基嘧啶-2-基)氧基]-3-氟苯基}-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 0.7 Hz, 1H), 8.24 (s, 1H), 7.56 (t, J = 0.8 Hz, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.14 (dd, J = 11.4, 2.0 Hz, 1H), 7.07 - 6.99 (m, 2H), 6.16 (s, 1H), 4.42 (s, 1H), 3.49 (s, 3H), 2.33 (s, 6H), 2.00 (s, 3H).	480.35
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.42 (s, 1H), 8.22 (s, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.22 - 7.14 (m, 2H), 7.02 (ddd, J = 8.4, 2.3, 0.9 Hz, 1H), 6.09 (s, 2H), 4.82 (d, J = 0.7 Hz, 1H), 4.13 (p, J = 6.7 Hz, 1H), 2.39 (s, 3H), 1.99 (d, J = 2.1 Hz, 3H), 1.61 (d, J = 6.8 Hz, 3H), 1.51 (d, J = 6.7 Hz, 3H).	512.35
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺 **滞转异构体 1**		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.42 (d, J = 5.1 Hz, 1H), 8.36 (s, 1H), 8.23 (s, 1H), 7.29 (t, J = 8.2 Hz, 1H), 7.19 - 7.05 (m, 3H), 4.29 (p, J = 6.9 Hz, 1H), 4.19 (d, J = 0.8 Hz, 1H), 2.49 (s, 3H), 2.10 (d, J = 2.2 Hz, 3H), 1.72 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H).	512.35

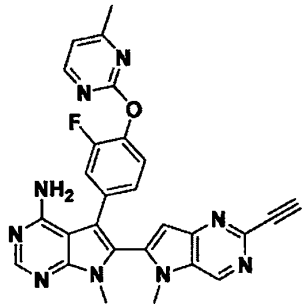
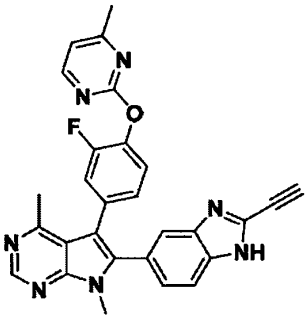
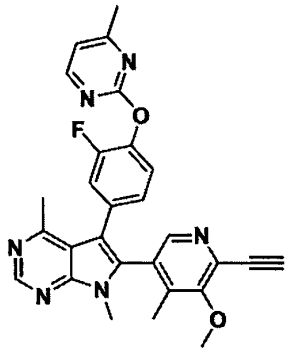
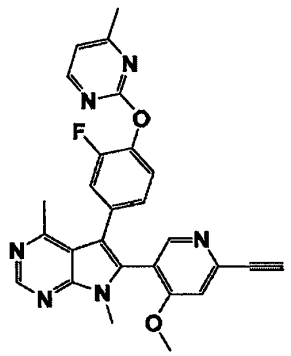
[1666]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-异丙基-7H-吡咯并[2,3-d]嘧啶-4-胺	 滞转异构体 2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.43 (s, 1H), 8.23 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.22 - 7.13 (m, 2H), 7.02 (dd, J = 8.3, 2.1 Hz, 1H), 5.93 (d, J = 130.2 Hz, 1H), 4.82 (s, 1H), 4.14 (p, J = 6.7 Hz, 1H), 2.40 (s, 3H), 2.00 (d, J = 2.1 Hz, 3H), 1.62 (d, J = 6.8 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H).	512.40
6-(6-乙炔基-4,5-二甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.33 (s, 1H), 8.24 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.21 - 7.13 (m, 2H), 7.07 - 6.99 (m, 1H), 6.14 (s, 1H), 4.58 (s, 1H), 3.44 (s, 3H), 2.40 (d, J = 3.2 Hz, 6H), 2.00 (s, 3H).	480.30
6-(6-乙炔基-5-甲氧基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d6) δ8.79 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 1.7 Hz, 1H), 7.57 (d, J = 1.7 Hz, 1H), 7.41- 7.36 (m, 2H), 7.22 -7.14 (m, 2H), 4.56 (s, 1H), 3.80 (s, 6H), 2.41 (d, J = 6.3 Hz, 6H).	481.20
6-(2-乙炔基喹喏啉-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ9.04 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.85 (dd, J = 8.6, 2.0 Hz, 1H), 7.38-7.24 (m, 2H), 7.20-7.11 (m, 2H), 4.90 (s, 1H), 3.71 (s, 3H), 2.38 (s, 3H), 1.15 (s, 1H).	503.15

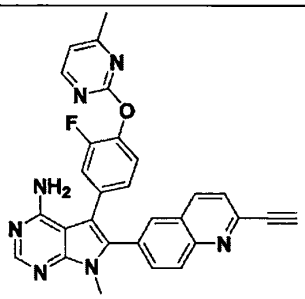
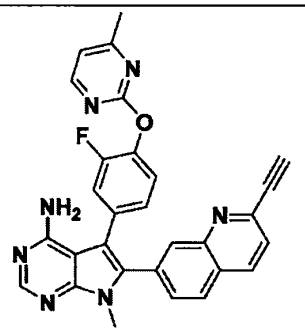
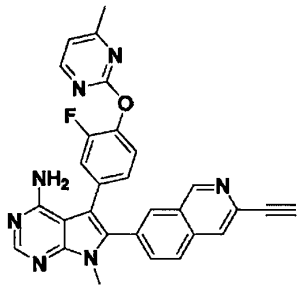
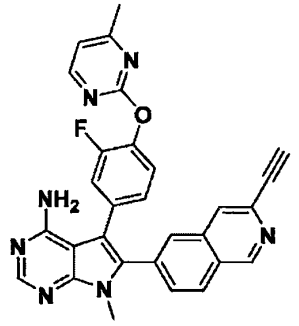
[1667]

化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基喹唑啉-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 9.59 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.26 (d, J = 2.0 Hz, 2H), 8.05 - 7.91 (m, 2H), 7.35 - 7.21 (m, 2H), 7.20 - 7.09 (m, 2H), 6.12 (s, 2H), 4.51 (s, 1H), 3.70 (s, 3H), 2.38 (s, 3H).	503.15
6-(3-乙炔基喹啉-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.15 - 8.08 (m, 2H), 7.83 (dd, J = 8.6, 1.9 Hz, 1H), 7.33 (t, J = 8.3 Hz, 1H), 7.28 (dd, J = 11.4, 2.0 Hz, 1H), 7.18 - 7.12 (m, 2H), 6.10 (s, 2H), 4.88 (s, 1H), 3.71 (s, 3H), 2.38 (s, 3H).	503.15
6-(2-乙炔基喹唑啉-7-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.74 (dd, J = 8.4, 1.7 Hz, 1H), 7.38 - 7.24 (m, 2H), 7.20 - 7.10 (m, 2H), 6.12 (s, 1H), 4.49 (s, 1H), 3.71 (s, 3H), 2.38 (s, 3H).	503.35
2'-乙炔基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7,7'-二甲基-7H,7'H-[6,6'-联吡咯并[2,3-d]嘧啶]-4-胺		^{1}H NMR (400 MHz, DMSO-d_6)9.07 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.29 (s, 1H), 7.34 (t, J = 8.2 Hz, 1H), 7.25 (d, J = 11.2 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.10 (d, J = 11.7 Hz, 2H), 4.25 (s, 1H), 3.62 (s, 3H), 3.31 (s, 3H), 2.41 (s, 3H).	506.20

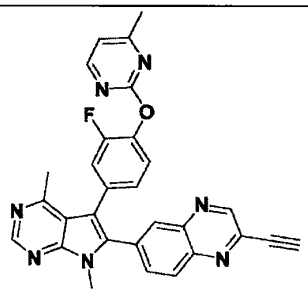
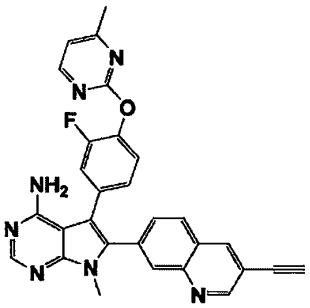
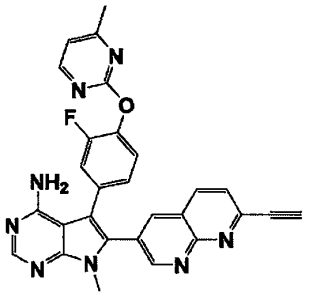
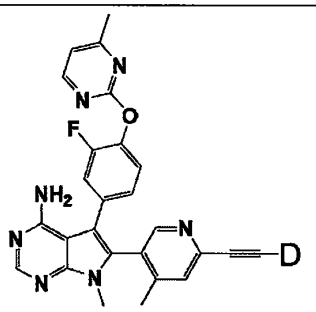
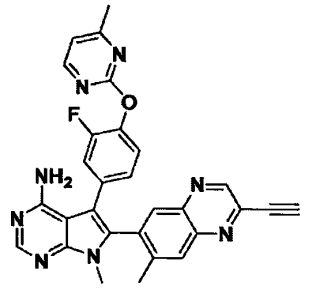
[1668]

化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基-5-甲基-5H-吡咯并[3,2-d]嘧啶-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.30 (s, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.26 (dd, J = 11.3, 2.1 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 7.11 (dd, J = 7.9, 1.9 Hz, 1H), 7.07 (s, 1H), 4.11 (s, 1H), 3.63 (s, 3H), 3.46 (s, 3H), 2.40 (s, 3H).	506.25
6-(2-乙炔基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ13.36 (d, J = 16.4 Hz, 1H), 8.75 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 7.77-7.67 (m, 1H), 7.53 (d, J = 9.6 Hz, 1H), 7.38 -7.23 (m, 3H), 7.17 (d, J = 5.0 Hz, 2H), 4.72 (s, 1H), 3.69 (d, J = 3.6 Hz, 3H), 2.38 (q, J = 2.0 Hz, 6H).	490.30
6-(6-乙炔基-5-甲氧基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6)8.79 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.35 (s, 1H), 7.38-7.27 (m, 2H), 7.18 (d, J = 5.0 Hz, 1H), 7.11 (dd, J = 8.4, 2.0 Hz, 1H), 4.64 (s, 1H), 3.85 (s, 3H), 3.60 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H), 1.97 (s, 3H).	495.20
6-(6-乙炔基-4-甲氧基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.29 (s, 1H), 7.42 (s, 1H), 7.36 - 7.27 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.14 - 7.07 (m, 1H), 4.48 (s, 1H), 3.87 (s, 3H), 3.61 (s, 3H), 2.41 (s, 6H).	481.15

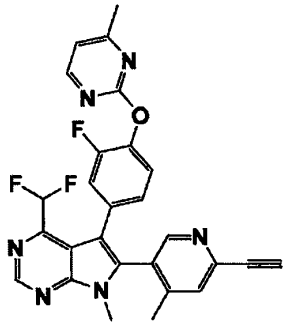
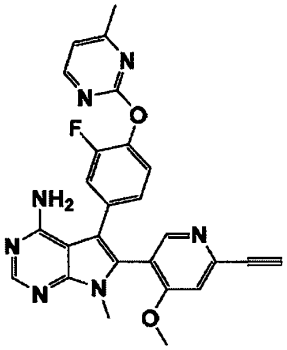
[1669]

化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基喹啉-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 5.0 Hz, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.09 (d, J = 2.0 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 8.3 Hz, 1H), 7.24 (dd, J = 11.3, 2.0 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.15 - 7.09 (m, 1H), 6.08 (s, 1H), 4.56 (s, 1H), 3.69 (s, 3H), 2.39 (s, 3H).	502.20
6-(2-乙炔基喹啉-7-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) 8.48 -8.41 (m, 2H), 8.26 (s, 1H), 8.04 (dd, J = 5.1, 3.3 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 8.5, 1.6 Hz, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.26 (dd, J = 11.3, 2.0 Hz, 1H), 7.19 -7.11 (m, 2H), 6.08 (s, 1H), 4.54 (s, 1H), 3.69 (s, 3H), 2.38 (s, 3H).	502.20
6-(3-乙炔基异喹啉-7-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 9.28 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.22 (d, J = 1.7 Hz, 1H), 8.14 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.76 (dd, J = 8.5, 1.7 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.24 (dd, J = 11.4, 2.1 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.12 (dd, J = 8.4, 2.0 Hz, 1H), 4.39 (s, 1H), 3.69 (s, 3H), 2.39 (s, 3H)	502.35
6-(3-乙炔基异喹啉-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 9.33 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 15.7 Hz, 2H), 7.69 (dd, J = 8.7, 1.5 Hz, 1H), 7.32 (t, J = 8.3 Hz, 1H), 7.24 (d, J = 11.0 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.14 - 7.08 (m, 1H),6.2-5.4(s,1H), 4.37 (s, 1H), 3.69 (s, 3H), 2.39 (s, 3H).	502.25

[1670]

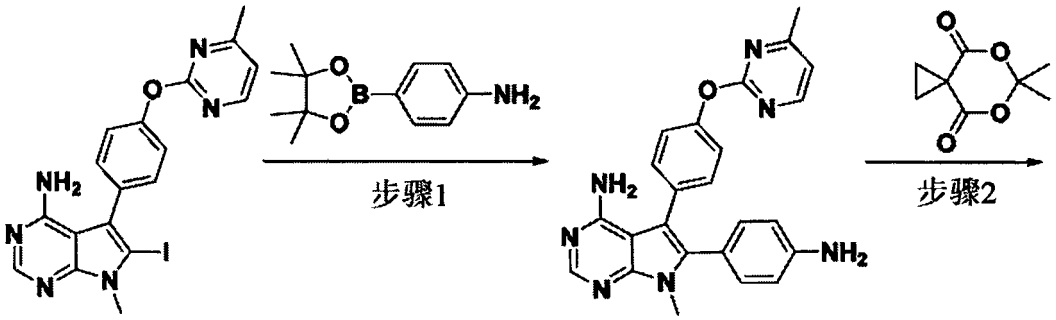
化合物	结构	质子 NMR	MS [M+1]
2-乙炔基-6-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)喹喏啉		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.81 (s, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.24 (d, J = 1.9 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.92 (dd, J = 8.7, 2.0 Hz, 1H), 7.43 (dd, J = 11.3, 2.0 Hz, 1H), 7.31 (t, J = 8.3 Hz, 1H), 7.24 - 7.14 (m, 2H), 4.91 (s, 1H), 3.81 (s, 3H), 2.42 (s, 3H), 2.38 (s, 3H).	502.35
6-(3-乙炔基喹啉-7-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) 8.93 (d, J = 2.1 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.09 - 8.00 (m, 2H), 7.63 (dd, J = 8.5, 1.7 Hz, 1H), 7.36-7.24 (m, 2H), 7.21-7.11 (m, 2H), 6.07 (s, 2H), 4.58 (s, 1H), 3.69 (s, 3H), 2.38 (s, 3H).	502.20
6-(7-乙炔基-1,8-萘啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) 8.96 (d, J = 2.5 Hz, 1H), 8.66 (d, J = 2.5 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.30 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.39 - 7.27 (m, 2H), 7.21 - 7.11 (m, 2H), 6.00-6.72(s,1H), 4.70 (s, 1H), 3.75 (s, 3H), 2.40 (s, 3H).	503.25
6-(6-(乙炔基-d)-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.58 (d, J = 0.8 Hz, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.22 - 7.12 (m, 2H), 7.07 - 7.01 (m, 1H), 6.14 (s, 1H), 3.47 (s, 3H), 2.41 (s, 3H), 2.02 (s, 3H).	467.20
6-(2-乙炔基-7-甲基喹喏啉-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.42 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 7.30 - 7.20 (m, 2H), 7.15 (d, J = 5.1 Hz, 1H), 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 6.12 (s, 1H), 4.88 (s, 1H), 3.48 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H).	517.20

[1671]

化合物	结构	质子 NMR	MS [M+1]
4-(二氟甲基)-6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶		1H NMR (400 MHz, DMSO-d6) 9.06 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.44 (s, 1H), 7.56 (dd, J = 11.2, 2.0 Hz, 1H), 7.50 -7.41 (m, 2H), 7.28 (ddd, J = 8.3, 2.1, 0.9 Hz, 1H), 7.21 (d, J = 5.1 Hz, 1H), 6.73 (s, 1H), 4.34 (s, 1H), 3.84 (s, 3H), 2.42 (s, 3H), 1.96 (s, 3H).	501.15
6-(6-乙炔基-4-甲氧基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.22 (d, J = 1.6 Hz, 2H), 7.39 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.22 - 7.12 (m, 2H), 7.03 (d, J = 7.9 Hz, 1H), 6.07 (s, 2H), 4.45 (s, 1H), 3.85 (s, 3H), 3.51 (s, 3H), 2.42 (s, 3H).	482.15

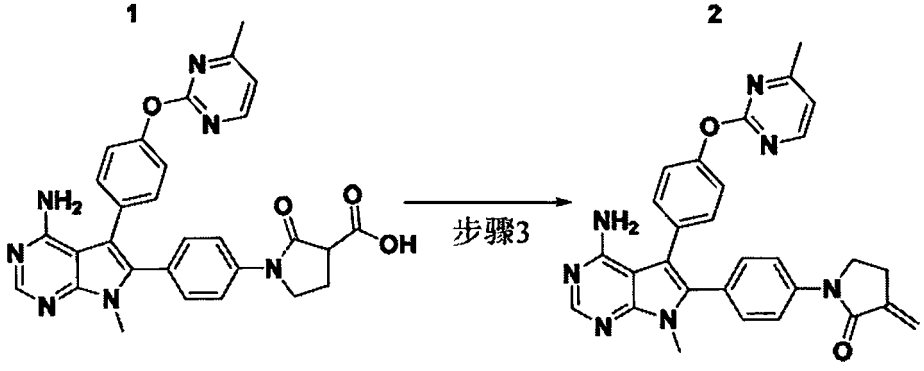
[1672] 实例29

[1673] 流程26



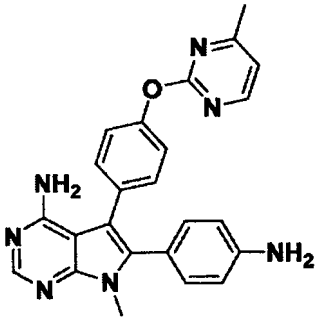
1 2

[1674]



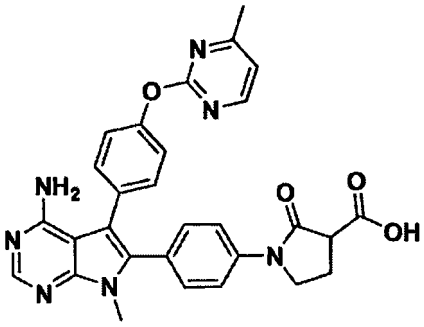
3

[1675] 6-(4-氨基苯基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1676] 

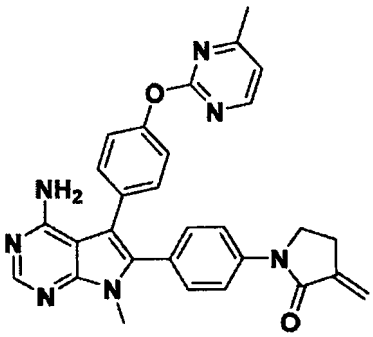
[1677] 步骤1:向圆底烧瓶中装入6-碘-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(5g,10.9mmol)、4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯胺(3.1g,14.2mmol)、Pd(dppf)Cl2(804mg,1.1mmol)、K3PO4(6.9g,32.7mmol)、DMF/H2O(16∶1,50mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物1小时。冷却后,混合物用水稀释,用DCM萃取,经Na_2SO_4干燥,真空蒸发,残余物用ACN(50mL)溶解且过滤,滤饼用ACN洗涤,在减压下干燥,得到呈灰白色固体状的6-(4-氨基苯基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(3g,65%)。

[1678] 1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-侧氧基吡咯烷-3-甲酸

[1679] 

[1680] 步骤2:向圆底烧瓶中装入6-(4-氨基苯基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(3g,7mmol)、6,6-二甲基-5,7-二氧杂螺[2.5]辛烷-4,8-二酮(2.38g,14mmol)、EtOH(50mL)及搅拌棒。在90℃下搅拌混合物整夜。真空蒸发溶剂,残余物用EA(50mL)洗涤且过滤,滤饼用ACN洗涤,在减压下干燥,得到呈灰白色固体状的1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-侧氧基吡咯烷-3-甲酸(2g,53%)。

[1681] 1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮

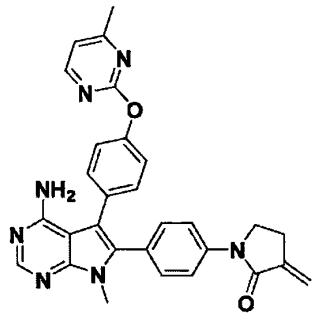
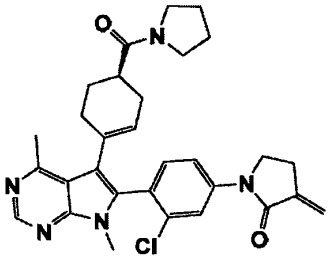
[1682] 

[1683] 步骤3:向圆底烧瓶中装入1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧

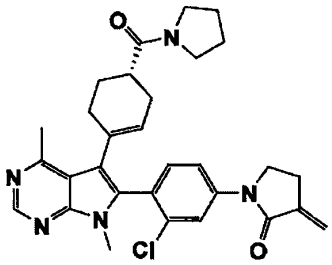
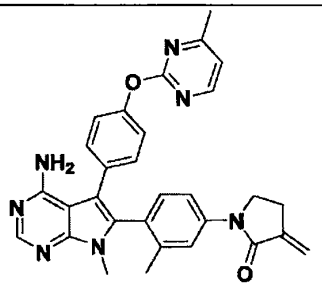
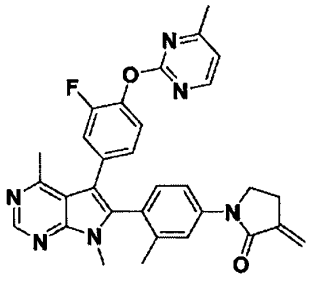
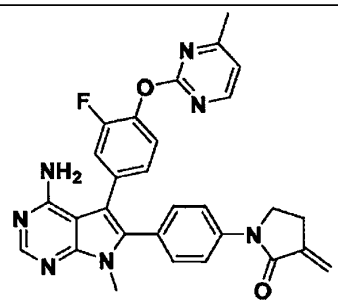
基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-2-侧氧基吡咯烷-3-甲酸(2g,3.73mmol)、HCHO水溶液(0.46g,5.6mmol)、二乙胺(0.54g,7.46mmol)及DMF(30mL)、搅拌棒。在90℃下搅拌混合物2小时。冷却后,混合物用水稀释,用DCM萃取,经Na_2SO_4干燥,真空蒸发,残余物通过硅胶柱色谱(用DCM/MeOH(50:1~10:1)洗脱)来纯化。通过制备型HPLC纯化粗产物,得到呈灰白色固体状的1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮(150mg)。

[1684] 根据实例29的方法制备的其它化合物描绘于下表28中。

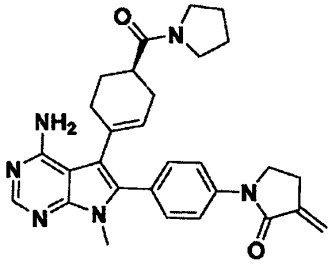
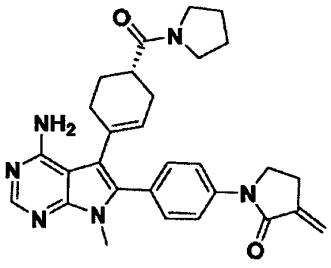
[1685] 表28.其它示例性化合物

化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.41 (d, J = 5.1 Hz, 1H), 8.22 (s, 1H), 7.84 (t, J = 8.0 Hz, 2H), 7.44 - 7.34 (m, 4H), 7.20 - 7.11 (m, 3H), 6.06 (s, 1H), 5.53 (d, J = 2.7 Hz, 1H), 4.45 (d, J = 2.8 Hz, 1H), 3.97 (t, J = 6.9 Hz, 1H), 3.72 (s, 3H), 2.97 (s, 1H), 2.50 (s, 3H), 1.94 (d, J = 2.1 Hz, 1H), 1.32 (t, J = 7.3 Hz, 1H).	504.20
[1686] (R)-1-(3-氯-4-(4,7-二甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮		1H NMR (400 MHz, DMSO-d6) δ 8.68 (s, 1H), 8.23 (dd, J = 4.9, 2.2 Hz, 1H), 7.86 (ddd, J = 8.6, 2.3, 1.4 Hz, 1H), 7.54 (dd, J = 9.6, 8.5 Hz, 1H), 5.98 (td, J = 2.8, 1.0 Hz, 1H), 5.69 (dd, J = 9.5, 4.3 Hz, 1H), 5.55 (dt, J = 3.0, 1.5 Hz, 1H), 3.96 (qt, J = 9.7, 4.9 Hz, 2H), 3.50 (d, J = 6.3 Hz, 3H), 3.43 (td, J = 6.7, 5.1 Hz, 2H), 3.26 (t, J = 6.8 Hz, 2H), 2.91 (tt, J = 5.9, 2.6 Hz, 2H), 2.67 (d, J = 1.5 Hz, 3H), 2.36 - 1.69 (m, 10H), 1.48 (ddt, J = 29.8, 12.3, 6.6 Hz, 1H).	530.25

[1687]

化合物	结构	质子 NMR	MS [M+1]
(S)-1-(3-氯-4-(4,7-二甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮		1H NMR (400 MHz, DMSO-d6) δ 8.68 (s, 1H), 8.23 (dd, J = 4.9, 2.2 Hz, 1H), 7.86 (ddd, J = 8.5, 2.3, 1.4 Hz, 1H), 7.54 (dd, J = 9.6, 8.5 Hz, 1H), 5.98 (td, J = 2.8, 1.0 Hz, 1H), 5.69 (dd, J = 10.6, 4.1 Hz, 1H), 5.55 (td, J = 2.6, 1.0 Hz, 1H), 3.96 (qt, J = 9.7, 4.9 Hz, 2H), 3.50 (d, J = 6.3 Hz, 3H), 3.47 - 3.39 (m, 2H), 3.26 (t, J = 6.9 Hz, 2H), 2.96 - 2.86 (m, 2H), 2.67 (d, J = 1.6 Hz, 3H), 2.29 - 1.69 (m, 10H), 1.46 (dtt, J = 29.5, 12.2, 6.7 Hz, 1H).	530.25
1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.22 (s, 1H), 7.76 - 7.72 (m, 2H), 7.40(d, J = 8.4Hz, 1H), 7.26 (t, J= 8.4Hz, 2H), 7.16 - 7.13(m, 3H), 5.92 (s, 1H), 5.77 (s, 1H), 3.90 (t, J = 13.6 Hz, 2H), 3.43 (s, 3H), 2.87 (t, J = 13.6 Hz, 2H), 2.40 (s, 3H), 2.01 (s, 3H).	518.20
1-(4-(5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)-3-亚甲基吡咯烷-2-酮		1H NMR: 1H NMR (400 MHz, DMSO-d6) 8.75 (s, 1H), 8.47 (d, J = 5.0 Hz, 1H), 7.82-7.73 (m, 2H), 7.45 (d, J = 8.4 Hz, 1H), 7.35-7.25 (m, 2H), 7.20-7.11 (m, 2H), 5.96-5.90 (m, 1H), 5.52-5.47 (m, 1H), 3.90 (t, J = 6.8 Hz, 2H), 3.52 (s, 3H), 2.88 (d, J = 14.1 Hz, 0H), 2.88 (s, 2H), 2.41 (d, J = 6.4 Hz, 6H), 2.05 (s, 3H).	535.40
1-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.89 - 7.84 (m, 2H), 7.48 - 7.40 (m, 2H), 7.35 (t, J = 8.4 Hz, 1H), 7.24 - 7.07 (m, 3H), 5.93 (dt, J = 2.8, 1.7 Hz, 1H), 5.49 (dt, J = 3.0, 1.5 Hz, 1H), 3.90 (t, J = 6.9 Hz, 2H), 3.61 (s, 3H), 2.88 (dt, J = 7.1, 3.6 Hz, 2H), 2.42 (s, 3H).	522.20

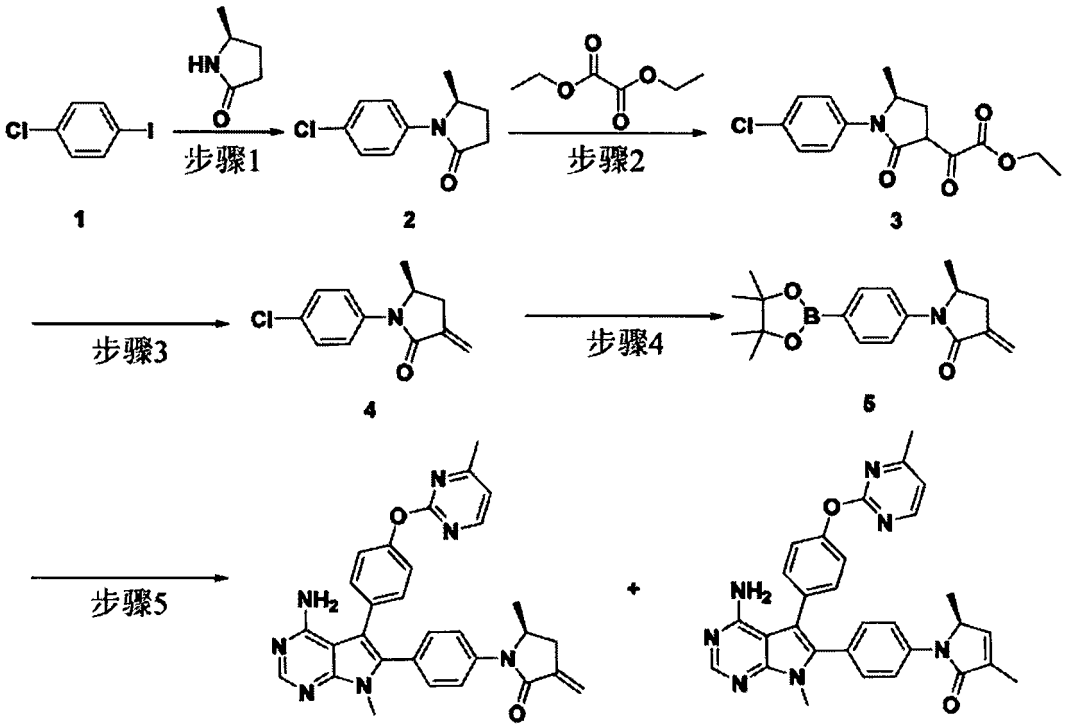
[1688]

化合物	结构	质子 NMR	MS [M+1]
(R)-1-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 16.6 Hz, 1H), 7.98 - 7.91 (m, 2H), 7.60 - 7.50 (m, 2H), 6.55 (s, 1H), 5.94 (q, J = 2.4 Hz, 1H), 5.78 (d, J = 3.7 Hz, 1H), 5.50 (q, J = 1.9 Hz, 1H), 3.94 (t, J = 6.9 Hz, 2H), 3.59 (s, 3H), 3.51 (dt, J = 10.1, 6.7 Hz, 1H), 3.48 - 3.40 (m, 1H), 3.32 - 3.26 (m, 1H), 3.25 (d, J = 5.6 Hz, 1H), 2.91 (d, J = 6.8 Hz, 2H), 2.84 (t, J = 5.8 Hz, 1H), 2.36 - 2.17 (m, 2H), 1.88 (dd, J = 13.4, 6.7 Hz, 4H), 1.76 (p, J = 6.8 Hz, 2H), 1.64 (d, J = 6.0 Hz, 2H).	497.20
(S)-1-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 14.7 Hz, 1H), 7.98 - 7.87 (m, 2H), 7.61 - 7.53 (m, 2H), 7.05 (d, J = 26.7 Hz, 1H), 5.94 (td, J = 2.8, 1.1 Hz, 1H), 5.86 - 5.73 (m, 1H), 5.51 (td, J = 2.5, 1.0 Hz, 1H), 3.94 (t, J = 6.9 Hz, 2H), 3.62 (s, 3H), 3.52 (dt, J = 10.1, 6.6 Hz, 1H), 3.43 (dt, J = 10.0, 6.8 Hz, 1H), 3.30 (d, J = 7.0 Hz, 1H), 3.28 - 3.21 (m, 1H), 2.95 - 2.80 (m, 3H), 2.38 - 2.15 (m, 2H), 1.88 (h, J = 6.5, 5.6 Hz, 4H), 1.81 - 1.55 (m, 4H).	497.15

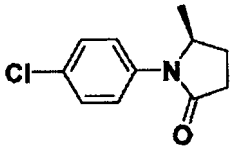
[1689] 实例30

[1690] 流程27

[1691]

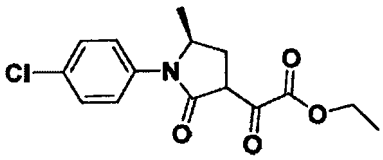


[1692] (S)-1-(4-氯苯基)-5-甲基吡咯烷-2-酮

[1693] 

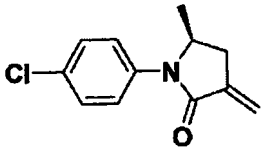
[1694] 步骤1:向可再密封的反应瓶中装入(5S)-5-甲基吡咯烷-2-酮(1g,10.0mmol)、1-氯-4-碘苯(3.57g,15.0mmol)、N1,N2-二甲基乙烷-1,2-二胺(196mg,2.00mmol)、CuI(191mg,1.00mmol)、CsF(9.78g,30.00mmol)、THF(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在25℃下搅拌混合物整夜。反应混合物用H_2O(10mL)稀释,且水相用EtOAc(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。通过硅胶柱色谱来纯化残余物。由此产生(S)-1-(4-氯苯基)-5-甲基吡咯烷-2-酮(1.91g,91%)。

[1695] 2-((5S)-1-(4-氯苯基)-5-甲基-2-侧氧基吡咯烷-3-基)-2-侧氧基乙酸乙酯

[1696] 

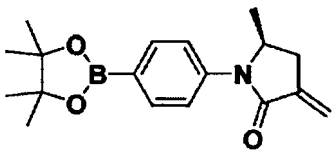
[1697] 步骤2:向可再密封的反应瓶中装入(5S)-1-(4-氯苯基)-5-甲基吡咯烷-2-酮(1g,4.76mmol)、乙二酸二乙酯(764mg,5.23mmol)、NaH(228mg,9.52mmol)、THF(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在80℃下搅拌混合物2小时。反应混合物用H2O(10mL)淬灭,且水相用EtOAc(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。通过硅胶柱色谱来纯化残余物。由此产生2-((5S)-1-(4-氯苯基)-5-甲基-2-侧氧基吡咯烷-3-基)-2-侧氧基乙酸乙酯(1.1g,74.8%)。

[1698] (S)-1-(4-氯苯基)-5-甲基-3-亚甲基吡咯烷-2-酮

[1699] 

[1700] 步骤3:向可再密封的反应瓶中装入2-[(5S)-1-(4-氯苯基)-5-甲基-2-侧氧基吡咯烷-3-基]-2-侧氧基乙酸乙酯(1.1g,3.55mmol)、(CH2O)n(513mg,17.7mmol)、Et2NH(657mg,10.6mmol)、DMF(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在100℃下搅拌混合物1小时。反应混合物用H_2O(10mL)稀释,且水相用EtOAc(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。通过硅胶柱色谱来纯化残余物。由此产生(S)-1-(4-氯苯基)-5-甲基-3-亚甲基吡咯烷-2-酮(300mg,38%)。

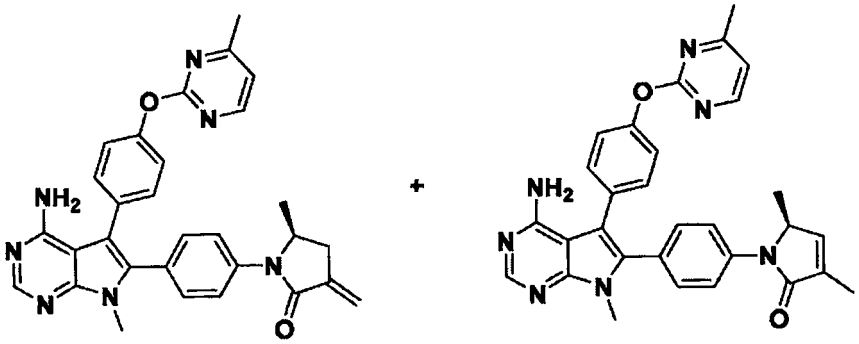
[1701] (S)-5-甲基-3-亚甲基-1-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)吡咯烷-2-酮

[1702] 

[1703] 步骤4:向可再密封的反应瓶中装入(5S)-1-(4-氯苯基)-5-甲基-3-亚甲基吡咯烷-2-酮(300mg,1.35mmol)、AcOK(396mg,4.05mmol)、Xphos-2G(155mg,135μmol)、Xphos(212mg,270μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷(8mL),且在90℃下

搅拌混合物2小时。反应混合物用H_2O(8mL)稀释,且水相用EtOAc(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。通过硅胶柱色谱来纯化残余物。由此产生(S)-5-甲基-3-亚甲基-1-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基)吡咯烷-2-酮(300mg,71%)。

[1704] (S)-1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-5-甲基-3-亚甲基吡咯烷-2-酮及(S)-1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3,5-二甲基-1,5-二氢-2H-吡咯-2-酮

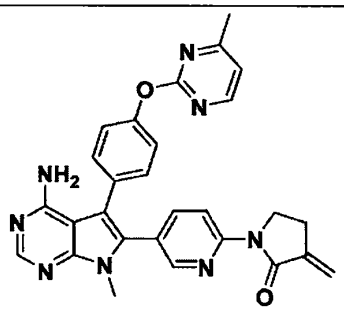
[1705] 

[1706] 步骤5:向可再密封的反应瓶中装入(5S)-5-甲基-3-亚甲基-1-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]吡咯烷-2-酮(200mg,638μmol)、6-碘-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(350mg,765μmol)、K3PO4(337mg,1.59mmol)、Pd(dppf)Cl2(46.6mg,63.8μmol)及搅拌棒,随后抽真空及用氮气吹扫三次。添加DME(5mL)及H2O(1mL),且在90℃下搅拌混合物2小时。反应混合物用H_2O(2mL)稀释,且水相用EtOAc(5mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型HPLC纯化(Hex(0.2%IPAmine):(EtOH:DCM=1:1)=50:50)。冻干产生呈白色无定形固体状的(5S)-1-[4-(4-氨基-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)苯基]-5-甲基-3-亚甲基吡咯烷-2-酮(2.5mg,0.7%)及呈白色无定形固体状的(5S)-1-[4-(4-氨基-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)苯基]-3,5-二甲基-2,5-二氢-1H-吡咯-2-酮(120.7mg,36.5%)。

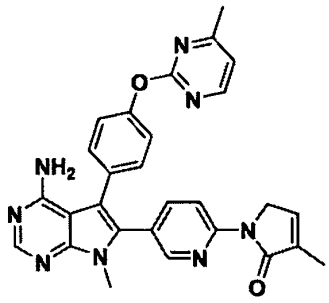
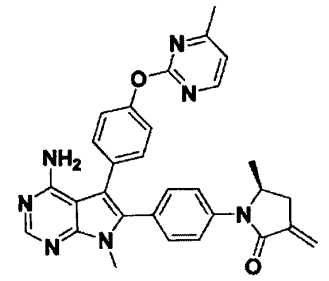
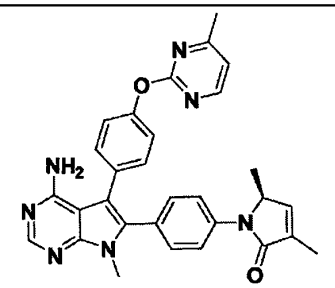
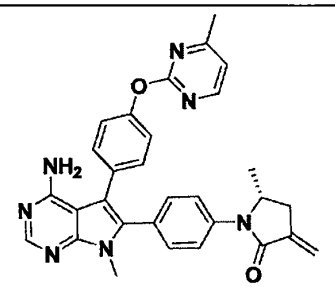
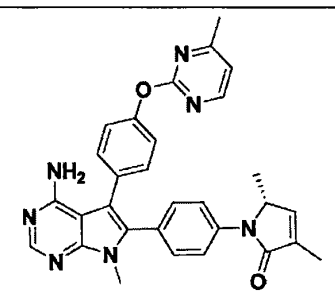
[1707] 根据实例30的方法制备的其它化合物描绘于下表29中。

[1708] 表29.其它示例性化合物

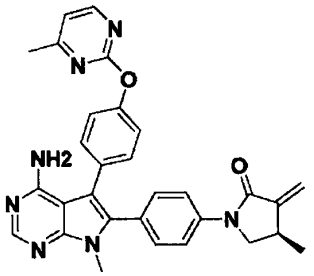
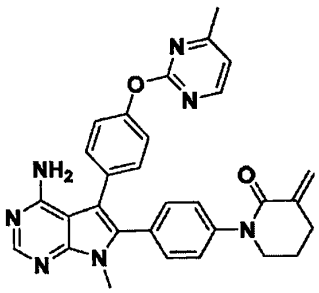
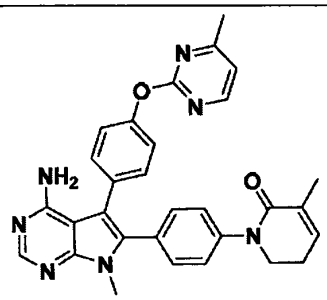
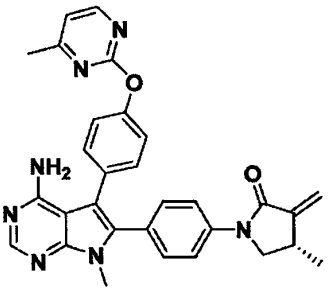
[1709]

化合物	结构	质子 NMR	MS [M+1]
1-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-2-基)-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d6) δ 8.54 - 8.44 (m, 2H), 8.40 - 8.39 (m, 1H), 8.23 (s, 1H), 7.94 - 7.92 (m, 1H), 7.37 - 7.29 (m, 2H), 7.25 - 7.18 (m, 2H), 7.16 (d, J = 5.0 Hz, 1H), 6.02 - 5.96 (m, 2H), 5.57 - 5.52 (m, 1H), 4.05 - 3.97 (m, 2H), 3.65 (s, 3H), 2.86 (s, 2H), 2.41 (s, 3H).	505.25

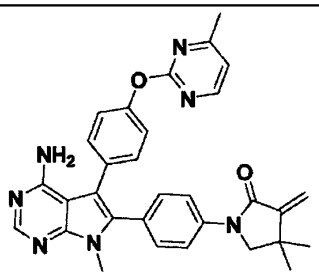
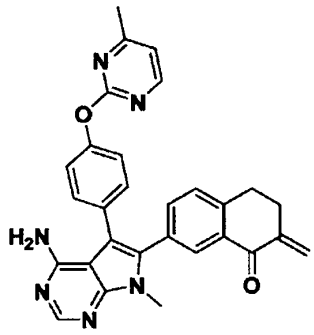
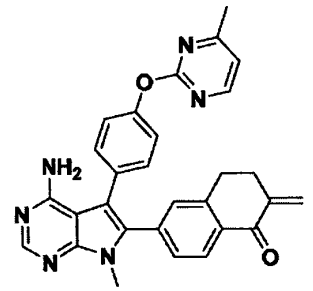
[1710]

化合物	结构	质子 NMR	MS [M+1]
1-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-2-基)-3-甲基-1,5-二氢-2H-吡咯-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.42-8.40 (m, 1H), 8.35-8.34 (m, 1H), 8.23 (s, 1H), 7.92-7.90 (m, 1H), 7.41 - 7.30 (m, 2H), 7.26 - 7.19 (m, 2H), 7.18 - 7.09 (m, 2H), 5.99 (s, 1H), 4.54 (q, J = 2.1 Hz, 2H), 3.64 (s, 3H), 2.41 (s, 3H), 1.86 (q, J = 1.9 Hz, 3H).	505.25
(S)-1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-5-甲基-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, 氯仿-d) δ 8.40 - 8.38 (m, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.34-7.17(m, 3H), 6.94 (d, J = 5.2 Hz, 2H), 6.81 (s, 2H), 5.12 (s, 2H), 4.65 (s, 1H), 3.78 (s, 3H), 2.53 (s, 3H), 2.06 - 1.91 (m, 2H), 1.29 (d, J = 6.7 Hz, 3H).	518.22
(S)-1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3,5-二甲基-1,5-二氢-2H-吡咯-2-酮		1H NMR (400 MHz, 甲醇-d4) δ 8.41 (d, J = 5.1 Hz, 1H), 8.22 (s, 1H), 7.62 - 7.59 (m, 2H), 7.47 - 7.36 (m, 4H), 7.18 - 7.02 (m, 3H), 7.03 (t, J = 1.8 Hz, 1H), 4.85-4.83(m, 1H), 3.73 (s, 3H), 2.50 (s, 3H), 1.94 (3, 3H), 1.25 (d, J = 6.7 Hz, 3H).	518.22
(R)-1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-5-甲基-3-亚甲基吡咯烷-2-酮		1H NMR (400 MHz, 氯仿-d) δ 8.42 - 8.36 (m, 2H), 7.64 - 7.56 (m, 2H), 7.37 - 7.29 (m, 4H), 7.23 - 7.15 (m, 2H), 6.94 (d, J = 5.0 Hz, 1H), 6.17 (s, 1H), 5.48 (s, 2H), 4.42-4.38 (m, 1H), 3.77 (s, 3H), 3.17-3.11 (m, 1H), 2.55-2.49 (m, 4H), 1.28 (d, J = 6.7 Hz, 3H).	518.22
(R)-1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3,5-二甲基-1,5-二氢-2H-吡咯-2-酮		1H NMR (400 MHz, 氯仿-d) δ 8.42 - 8.36 (m, 2H), 7.65 - 7.57 (m, 2H), 7.37 - 7.28 (m, 4H), 7.23 - 7.15 (m, 2H), 6.94 (d, J = 5.0 Hz, 1H), 5.48 (t, J = 2.1 Hz, 1H), 5.13 (s, 1H), 4.47 - 4.35 (m, 1H), 3.77 (s, 3H), 3.14 (s, 1H), 2.58 - 2.47 (m, 3H), 1.29 (d, J = 6.2 Hz, 3H).	518.22

[1711]

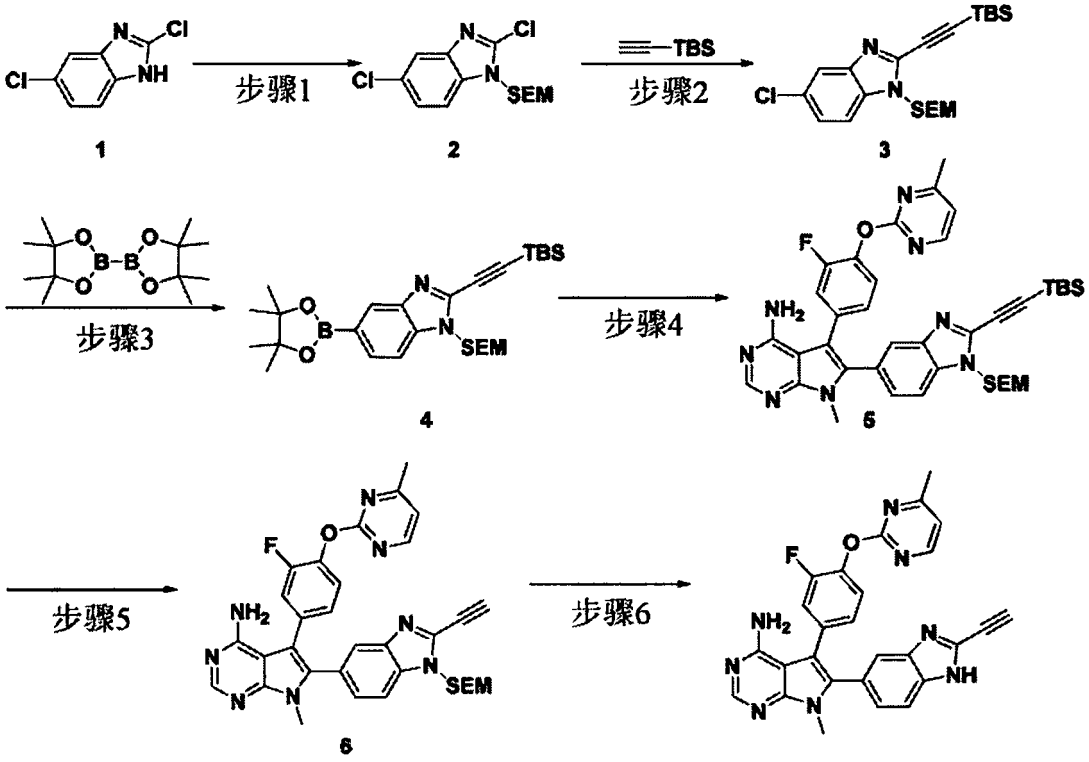
化合物	结构	质子 NMR	MS [M+1]
(R)-1-(4-(4-氨基-7-甲基-5-(4-((5-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-甲基-3-亚甲基吡咯烷-2-酮		1H NMR (400 MHz, 氯仿-d) δ 8.39 (d, J = 5.0 Hz, 2H), 7.83 -7.76 (m, 2H), 7.36 - 7.28 (m, 4H), 7.23 -7.16 (m, 2H), 6.94 (d, J = 5.0 Hz, 1H), 6.19 (d, J = 2.8 Hz, 1H), 5.45 (d, J = 2.5 Hz, 1H), 5.13 (s, 2H), 4.03 (dd, J = 9.4, 8.6 Hz, 1H), 3.75 (s, 3H), 3.44 (dd, J = 9.5, 5.6 Hz, 1H), 3.13 (s, 1H), 2.53 (s, 3H), 1.37 (d, J = 6.9 Hz, 3H).	518.35
1-(4-(4-氨基-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-亚甲基哌啶-2-酮		^{1}H NMR (400 MHz, DMSO-d_6)8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.40 (s, 4H), 7.36-7.29 (m, 2H), 7.23-7.13 (m, 3H), 6.18-5.74 (m, 2H), 5.41 (d, J = 2.2 Hz, 1H), 3.75 (t, J = 5.7 Hz, 2H), 3.63 (s, 3H), 2.74-2.61 (m, 2H), 2.41 (s, 3H), 1.95-1.93 (m, 2H).	518.25
1-(4-(4-氨基-7-甲基-5-(4-(4-甲基嘧啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-3-甲基-5,6-二氢吡啶-2(1H)-酮		^{1}H NMR (400 MHz, DMSO-d_6)8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.38 (s, 4H), 7.36-7.29 (m, 2H), 7.23-7.17 (m, 2H), 7.16 (d, J = 5.0 Hz, 1H), 6.69-6.46 (m, 1H), 5.89 (s, 1H), 3.82 (t, J = 6.8 Hz, 2H), 3.63 (s, 3H), 2.42-2.36 (m, 5H), 1.82-1.80 (m, 3H).	518.35
(S)-1-(4-(4-氨基-7-甲基-5-(4-((5-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4-甲基-3-亚甲基吡咯烷-2-酮		1H NMR (400 MHz, 氯仿-d) δ8.39 (d, J = 5.3 Hz, 2H), 7.82 - 7.62 (m, 2H), 7.36 -7.28 (m, 4H), 7.23 - 7.15 (m, 2H), 6.94 (d, J = 5.0 Hz, 1H), 6.18 (d, J = 2.9 Hz, 1H), 5.45 (d, J = 2.5 Hz, 1H), 5.11 (s, 2H), 4.03 (t, J = 9.0 Hz, 1H), 3.75 (s, 3H), 3.44 (dd, J = 9.4, 5.5 Hz, 1H), 3.12 (s, 1H), 2.52 (s, 3H), 1.36 (d, J = 6.9 Hz, 3H).	518.35

[1712]

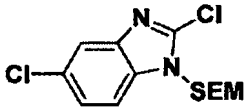
化合物	结构	质子 NMR	MS [M+1]
1-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)苯基)-4,4-二甲基-3-亚甲基吡咯烷-2-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.86 - 7.80 (m, 2H), 7.46 - 7.39 (m, 2H), 7.35 - 7.25 (m, 2H), 7.23 - 7.12 (m, 3H), 5.90 (s, 1H), 5.50 (s, 1H), 3.67 (s, 2H), 3.62 (s, 3H), 2.41 (s, 3H), 1.27 (s, 6H).	532.20
7-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-亚甲基-3,4-二氢萘-1(2H)-酮		1H NMR (400 MHz, DMSO-d6) δ 8.46 (1H, d), 8.22 (1H, s), 7.91 (1H, d), 7.60 (1H, dd), 7.44 (1H, d), 7.35-7.27 (2H, m), 7.22-7.10 (3H, m), 5.81 (3H, dd), 3.61 (3H, s), 3.02 (2H, t), 2.90-2.82 (2H, m), 2.40 (3H, s)	489.30
6-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-亚甲基-3,4-二氢萘-1(2H)-酮		1H NMR (400 MHz, DMSO-d6) δ 8.46 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.36 (dd, J = 8.0, 1.7 Hz, 1H), 7.35 -7.27 (m, 2H), 7.24-7.13 (m, 3H), 6.06 (d, J = 2.1 Hz, 1H), 5.99 (s, 2H), 5.56 (d, J = 2.0 Hz, 1H), 3.68 (s, 3H), 2.96 (t, J = 6.3 Hz, 2H), 2.84 (t, J = 6.1 Hz, 2H), 2.41 (s, 3H).	489.35

[1713] 实例31

[1714] 流程28

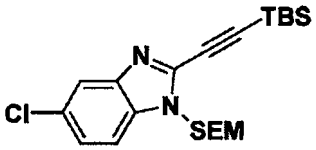
[1715] 

[1716] 2,5-二氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑

[1717] 

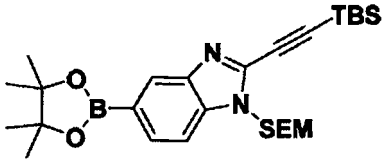
[1718] 步骤1:向圆底烧瓶中装入2,5-二氯-1H-苯并[d]咪唑(1g,5.4mmol)、二甲基甲酰胺(5mL)及搅拌棒,添加NaH(60%,259mg,6.48),且在0℃下搅拌溶液10分钟。添加SEMCl(896mg,5.4mmol),且在0℃下搅拌溶液10小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得混合物经由C18柱纯化。真空浓缩,产生呈黄色油状的2,5-二氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑(820mg,48%)。

[1719] 2-((叔丁基二甲基硅烷基)乙炔基)-5-氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑

[1720] 

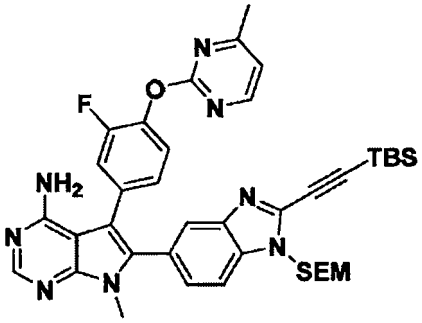
[1721] 步骤2:向圆底烧瓶中装入2,5-二氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑(800mg,1.30mmol)、叔丁基(乙炔基)二甲基硅烷(274mg,1.96mmol)、$Pd(PPh_3)_2Cl_2$(183mg,261μmol)、CuI(99mg,0.52mmol)、TEA(395mg,3.09mmol)及搅拌棒。添加二甲基甲酰胺(20mL),且在50℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得混合物经由C18柱纯化。真空浓缩,产生呈黄色油状的2-((叔丁基二甲基硅烷基)乙炔基)-5-氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑(500mg,47%)。

[1722] 2-((叔丁基二甲基硅烷基)乙炔基)-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑

[1723] 

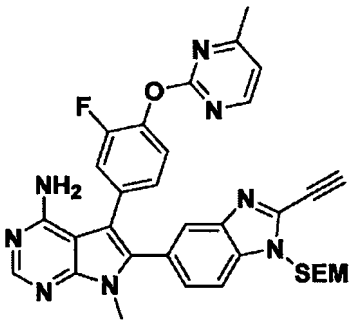
[1724] 步骤3:向圆底烧瓶中装入2-((叔丁基二甲基硅烷基)乙炔基)-5-氯-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑(480mg,1.14mmol)、4,4,4′,4′,5,5,5′,5′-八甲基-2,2′-双(1,3,2-二氧杂硼杂环戊烷)(579mg,2.28mmol)、Pd(dppf)Cl_2(83mg,114μmol)、AcOK(335mg,3.42mmol)及搅拌棒。添加二恶烷(10mL),且在90℃下搅拌溶液2小时。所得混合物经由C18柱纯化。真空浓缩,产生呈白色油状的2-((叔丁基二甲基硅烷基)乙炔基)-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑(550mg,94%)。

[1725] 6-(2-((叔丁基二甲基硅烷基)乙炔基)-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1726] 

[1727] 步骤4:向可再密封的反应瓶中装入2-((叔丁基二甲基硅烷基)乙炔基)-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑(480mg,0.86mmol)、5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(273mg,0.57mmol)、Pd(dppf)Cl_2(42mg,57μmol)、K_3PO_4(363mg,1.71mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME:水=10:1(10mL),且在90℃下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过制备型TLC纯化。真空浓缩,产生呈黄色无定形固体状的6-(2-((叔丁基二甲基硅烷基)乙炔基)-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(260mg,62%)。

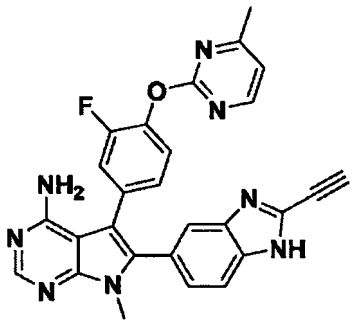
[1728] 6-(2-乙炔基-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1729] 

[1730] 步骤5:向圆底烧瓶中装入6-(2-乙炔基-1-((2-(三甲基硅烷基)乙氧基)甲基)-

1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(240mg,0.33mmol)、THF(4mL)及搅拌棒。添加TBAF(1M,0.7mL,0.66mmol),且在室温下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。通过硅胶柱色谱(用二氯甲烷/甲醇(8:1)洗脱)来纯化残余物。真空浓缩,产生呈黄色油状的6-(2-乙炔基-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(100mg,49%)。

[1731] 6-(2-乙炔基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

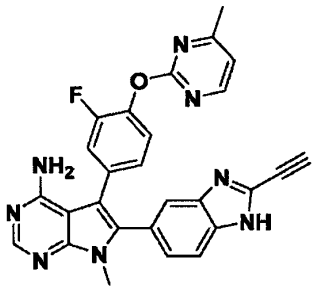
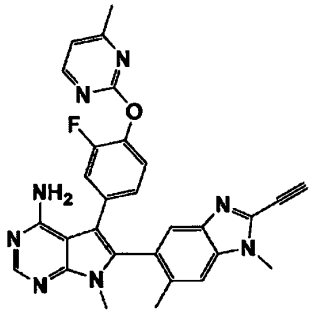
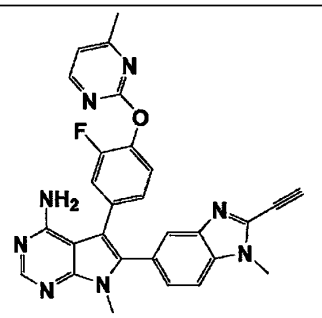
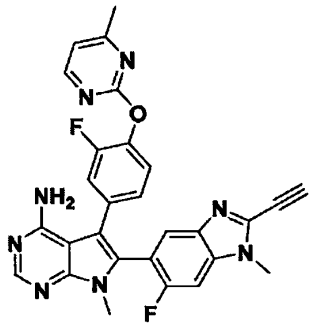
[1732] 

[1733] 步骤6:向圆底烧瓶中装入6-(2-乙炔基-1-((2-(三甲基硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(80mg,852μmol)、DCM(4mL)及搅拌棒。添加TFA(44mg,0.39mmol),且在室温下搅拌溶液1小时。使反应混合物处于真空中。所得粗物质通过制备型HPLC纯化(柱:YMC-Actus Triart C18,30*250,5um;移动相A:水(10MMOL/L NH_4HCO_3+0.1%$NH_3 \cdot H_2O$),移动相B:ACN;流量:50mL/min;梯度:30B至65B,历时8分钟;220nm;RT1:7.22)。冻干产生呈灰白色无定形固体状的6-(2-乙炔基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(22.1mg,35%)。

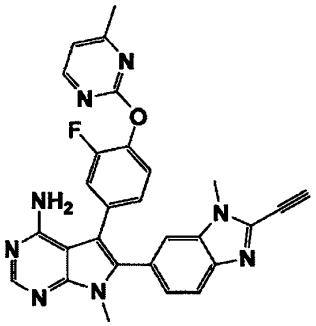
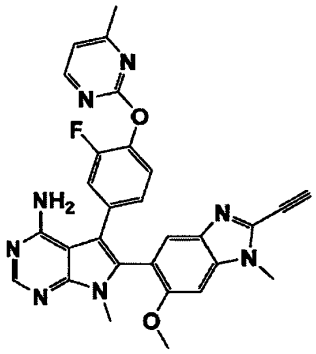
[1734] 根据实例31的方法制备的其它化合物描绘于下表30中。

[1735] 表30.其它示例性化合物

[1736]

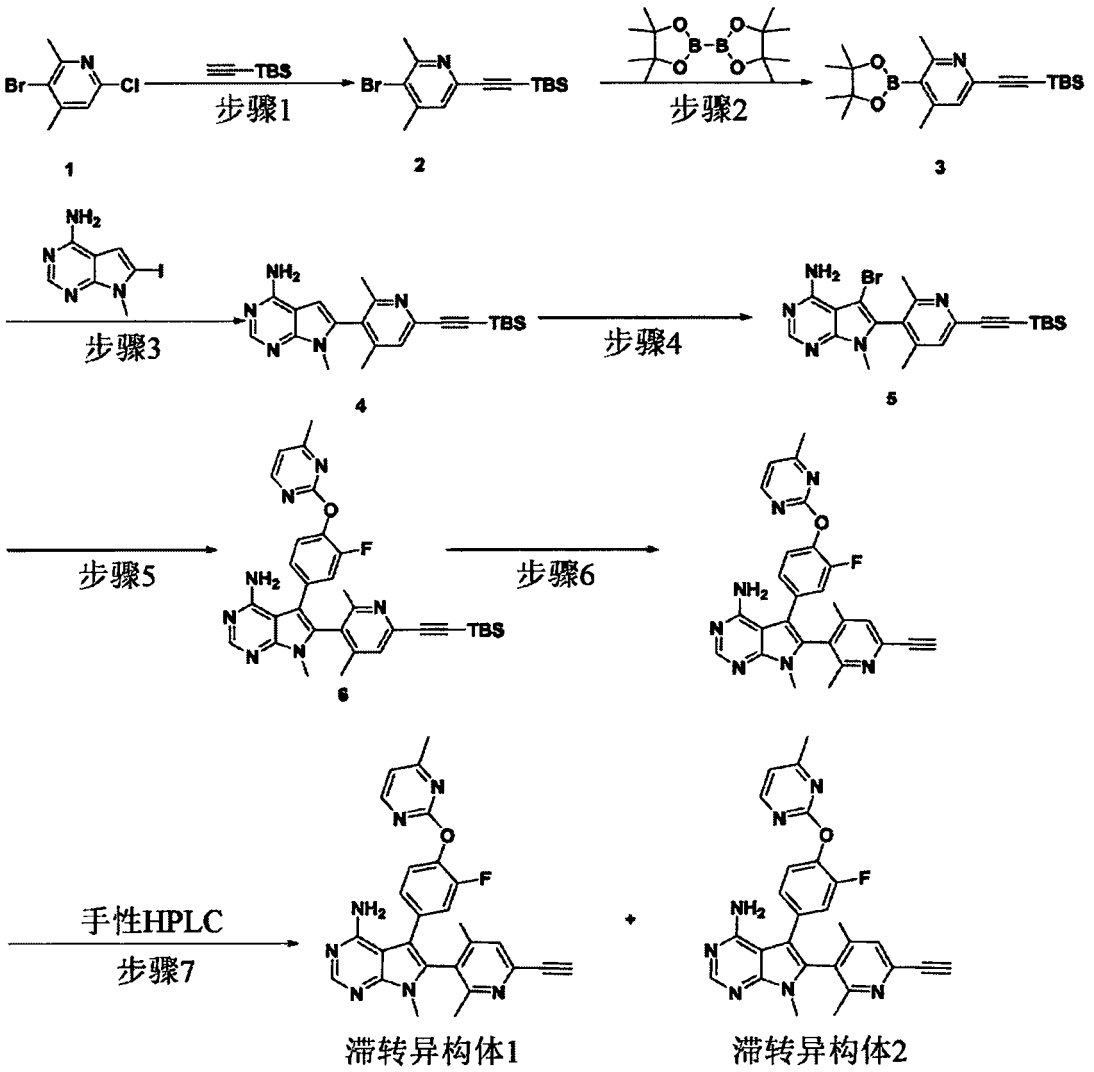
化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (300 MHz, DMSO-d6) δ 13.29 (s, 1H), 8.44 (s, 1H), 8.20 (s, 1H), 7.67 - 7.18 (m, 4H), 7.15 (d, J = 5.0 Hz, 3H), 4.67 (s, 1H), 3.61 (s, 3H), 2.38 (s, 3H).	491.20
6-(2-乙炔基-1,6-二甲基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.43 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 7.70 (s, 1H), 7.56 (s, 1H), 7.28 (t, J = 8.4 Hz,1H), 7.21 - 7.13 (m, 2H), 7.12 - 7.05 (m, 1H), 6.03 (s, 2H), 4.95 (s, 1H), 3.87 (s,3H), 2.38 (s, 3H), 2.12 (s, 3H).	519.25
6-(2-乙炔基-1-甲基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 5.2 Hz, 1H), 8.22 (s, 1H), 7.70 (d, J = 1.5 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.40 - 7.26 (m, 2H), 7.24 - 7.06 (m, 3H), 5.99 (s, 2H), 4.98 (s, 1H), 3.89 (s, 3H), 3.58 (s, 3H), 2.40 (s, 3H).	505.20
6-(2-乙炔基-6-氟-1-甲基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6)8.44 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.72 (dd, J = 9.8, 8.1 Hz, 2H), 7.30 (t, J = 8.4 Hz, 1H), 7.21 (dd, J = 11.3, 2.0 Hz, 1H), 7.16 (d, J = 5.1 Hz, 1H), 7.13-7.07 (m, 1H), 6.04 (s, 2H), 5.00 (s, 1H), 3.87 (s, 3H), 3.52 (s, 3H), 2.38 (s, 3H).	523.20

[1737]

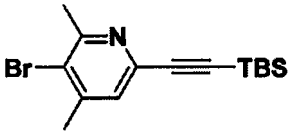
化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基-1-甲基-1H-苯并[d]咪唑-6-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.44 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.70 (d, J = 1.6 Hz, 1H), 7.65 (s, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.26 -7.14 (m, 3H), 7.14 -7.08 (m, 1H), 6.02 (s, 2H), 4.99 (s, 1H), 3.85 (s, 3H), 3.62 (s, 3H), 2.39 (s, 3H).	505.20
6-(2-乙炔基-6-甲氧基-1-甲基-1H-苯并[d]咪唑-5-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) 8.44 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.48 (s, 1H), 7.34 (s, 1H), 7.28 (t, J = 8.4 Hz, 1H), 7.18 -7.10 (m, 2H), 7.05 (dd, J = 8.4, 2.0 Hz, 1H), 5.99 (s, 2H), 4.91 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.44 (s, 3H), 2.38 (s, 3H).	535.20

[1738] 实例32

[1739] 流程29

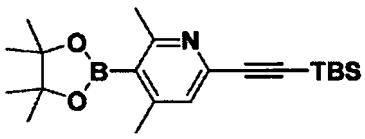
[1740] 

[1741] 3-溴-6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶

[1742] 

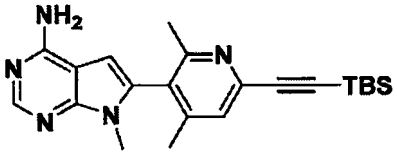
[1743] 步骤1:向可再密封的反应瓶中装入3-溴-6-氯-2,4-二甲基吡啶(8g,36.2mmol)、叔丁基(乙炔基)二甲基硅烷(5.58g,39.8mmol)、CuI(1.37g,7.24mmol)、$Pd(PPh_3)_2Cl_2$(2.54g,3.62mmol)、TEA(10.9g,108mmol)、二甲基甲酰胺(100mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在80℃下搅拌混合物2小时。反应混合物用水淬灭,用DCM萃取。合并有机相且用盐水洗涤三次,经Na_2SO_4干燥,真空蒸发。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈灰白色油状的3-溴-6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶(10.0g,85%)。

[1744] 6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基-3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶

[1745] 

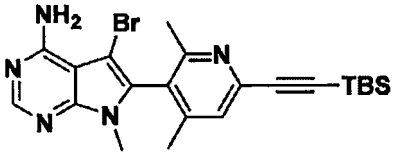
[1746] 步骤2:向可再密封的反应瓶中装入3-溴-6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶(9.6g,29.52mmol)、4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,3,2-二氧杂硼杂环戊烷(14.88g,59.04mmol)、$Pd(dppf)Cl_2$(2.15mg,2.95μmol)、AcOK(8.66g,88.44mmol)、二甲基甲酰胺(150mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物12小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,真空蒸发。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈灰白色无定形固体状的6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基-3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(2.5g,27%)。

[1747] 6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1748] 

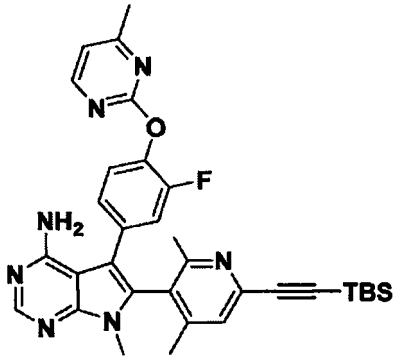
[1749] 步骤3:向可再密封的反应瓶中装入6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基-3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(1.3g,3.49mmol)、6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(952mg,3.49mmol)、双(金刚烷-1-基)(丁基)膦(125mg,349μmol)、2′-氨基-1,1′-联苯-2-基双(金刚烷-1-基)(丁基)膦氯化钯(1+)(233mg,349μmol)、K_3PO_4(2.2g,1.05mmol)、二恶烷/H_2O(15mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物6小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,真空蒸发。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色无定形固体状的6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,37%)。

[1750] 5-溴-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1751] 

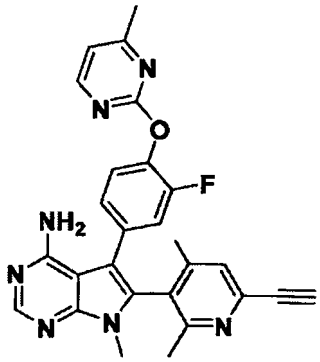
[1752] 步骤4:向圆底烧瓶中装入6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,1.27mmol)、NBS(272mg,1.53mmol)、二甲基甲酰胺(20mL)及搅拌棒。在室温下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,真空蒸发。所得粗物质通过硅胶色谱纯化(20g柱;用二氯甲烷/甲醇12:1洗脱)。真空浓缩,产生呈红色无定形固体状的5-溴-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,88.3%)。

[1753] 6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1754] 

[1755] 步骤5:向可再密封的反应瓶中装入5-溴-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(460mg,977μmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(643mg,1.95mmol)、$Pd(PPh_3)_4$(112mg,97.7μmol)、K_3PO_4(621mg,2.93mmol)、DME/H_2O(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物2小时。反应混合物用水淬灭,用DCM萃取。有机相用盐水洗涤三次,经Na_2SO_4干燥,真空蒸发。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈橙色无定形固体状的6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(250mg,43%)。

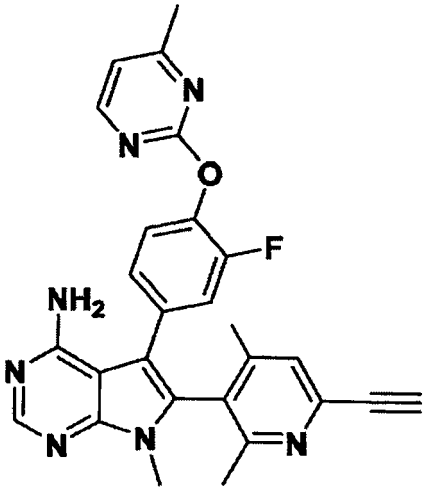
[1756] 6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1757] 

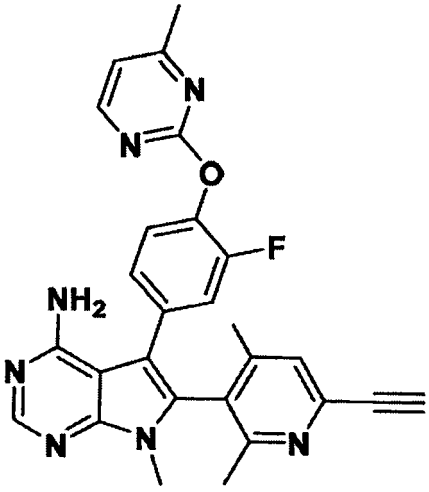
[1758] 步骤6:向圆底烧瓶中装入6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(230mg,387μmol)、CsF(176mg,1.16mmol)及搅拌棒。添加四氢呋喃(8mL),且在50℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过HPLC纯化(柱:XBridge Shield RP18 OBD柱,30*150mm,5um;移动相A:水(10MMOL/L NH_4HCO_3),移动相B:ACN;流量:60mL/min;梯度:20B至45B,历时8min;220nm;RT1:7.12;)。冻干产生呈灰白色无定形固体状的6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(100mg,208μmol)。

[1759] 6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1760]



峰1



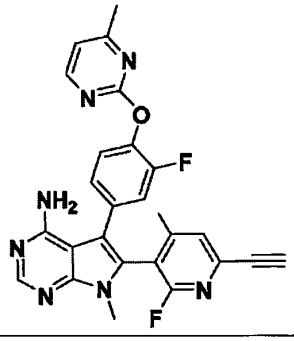
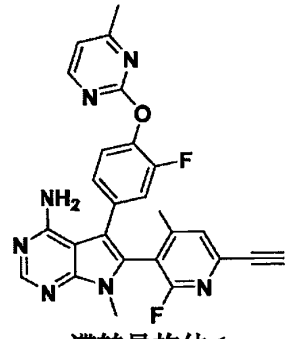
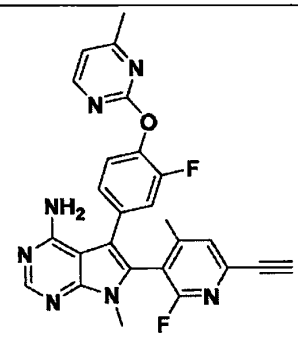
峰2

[1761] 步骤7:所得粗物质通过制备型手性HPLC来纯化(柱:DZ-CHIRALPAK IF-3,4.6*50mm,3um;移动相A:Hex(0.2%IPAmine):(EtOH:DCM=1:1)=75:25)。冻干产生呈灰白色无定形固体状的6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(峰1)(33.7mg,70.2μmol,33.7%);呈灰白色无定形固体状的6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(峰2)(25mg,52.1μmol,25%)。

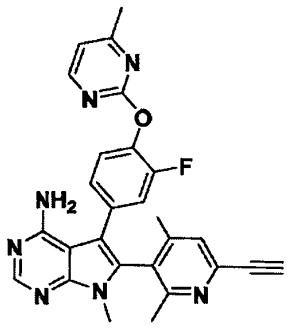
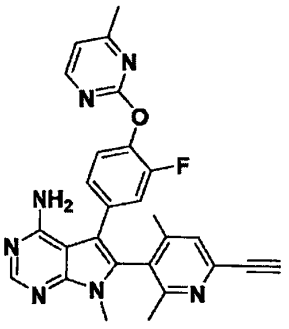
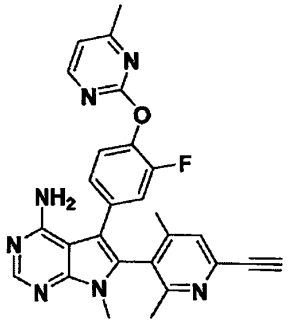
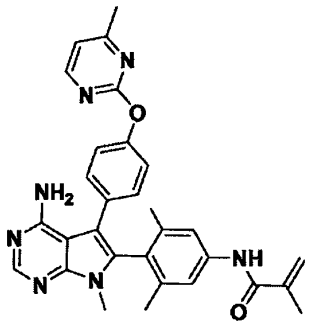
[1762] 根据实例32的方法制备的其它化合物描绘于下表31中。

[1763] 表31.其它示例性化合物

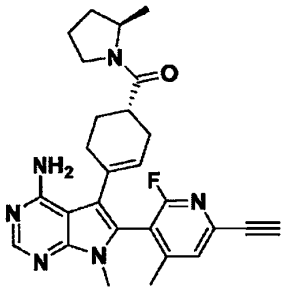
[1764]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (400 MHz, DMSO-d6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.59 (s, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.13 (dd, J = 11.3, 2.1 Hz, 1H), 7.01 - 6.96 (m, 1H), 6.21 (s, 1H), 4.59 (s, 1H), 3.49 (s, 3H), 2.41 (s, 3H), 2.02 (s, 3H).	484.15
6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺 **滞转异构体 1**		1H NMR (400 MHz, DMSO-d6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.59 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.14 (dd, J = 11.3, 2.1 Hz, 1H), 7.04 - 6.93 (m, 1H), 6.21 (s, 2H), 4.59 (s, 1H), 3.50 (s, 4H), 2.41 (s, 3H), 2.03 (s, 3H).	484.15
6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺 **滞转异构体 2**		1H NMR (400 MHz, DMSO-d6) δ 8.48 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.59 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.14 (dd, J = 11.3, 2.1 Hz, 1H), 7.04 - 6.93 (m, 1H), 6.21 (s, 2H), 4.59 (s, 1H), 3.50 (s, 4H), 2.41 (s, 3H), 2.03 (s, 3H).	484.15

[1765]

化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		1H NMR (300 MHz, DMSO-d6) 8.45 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.42 (s, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 7.05 (dd, J = 11.5, 2.0 Hz, 1H), 6.94 (dt, J = 8.3, 1.4 Hz, 1H), 6.16 (s, 1H), 4.35 (s, 1H),3.32(s,3H), 2.38 (s, 3H), 2.14 (s, 3H), 2.00 (s, 3H).	480.15
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺 滞转异构体 1		1H NMR (400 MHz, DMSO-d6) 8.47 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.44 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.07 (dd, J = 11.4, 2.1 Hz, 1H), 7.00 -6.93 (m, 1H), 6.15 (s, 2H), 4.36 (s, 1H), 3.34 (s, 3H), 2.41 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H).	480.15
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺 滞转异构体 2		1H NMR (400 MHz, DMSO-d6) 8.47 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.44 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 7.07 (dd, J = 11.4, 2.0 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.15 (s, 2H), 4.37 (s, 1H), 3.41 (s, 3H), 2.41 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H).	480.15
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.50 (s, 2H), 7.28 - 7.10 (m, 5H), 5.80 (m, 2H), 5.52 (s, 1H), 3.37 (s, 3H), 2.40 (s, 3H), 1.96 (m, 9H).	520.40

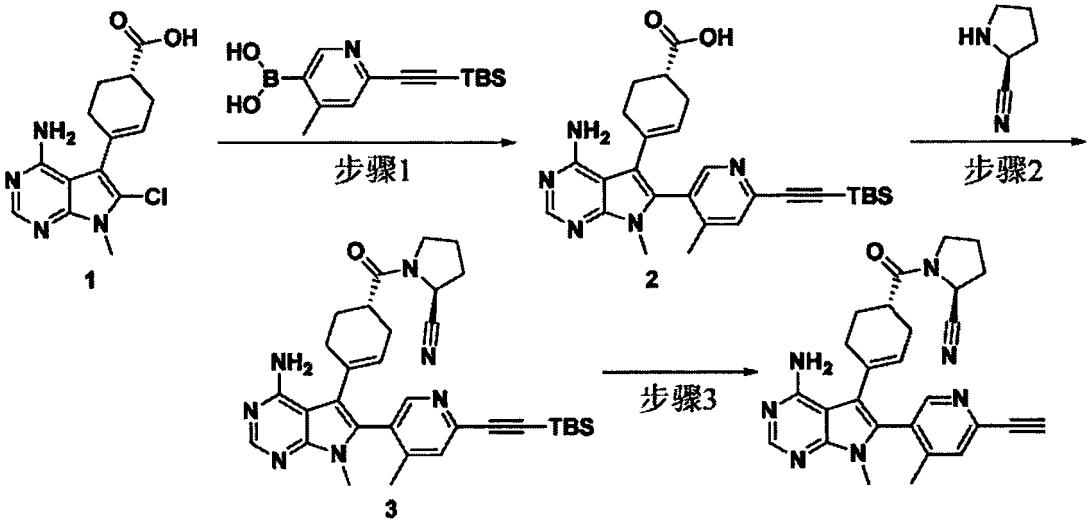
[1766]

化合物	结构	质子 NMR	MS [M+1]
((S)-4-(4-氨基-6-(6-乙炔基-2-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) δ 8.14 (t, J = 2.8 Hz, 1H), 7.65 (s, 1H), 6.61 (s, 2H), 5.61 (s, 1H), 4.60 (d, J = 1.1 Hz, 1H), 4.01(s,1H), 3.51 (d, J = 8.6 Hz, 2H), 3.46 - 3.36 (m, 3H), 2.71 (s, 1H), 2.17 (s, 5H), 1.91-1.80 (s, 5H), 1.62 (s, 1H), 1.49 (d, J = 5.0 Hz, 1H), 1.17 - 1.03 (m, 3H).	473.30

[1767] 实例33

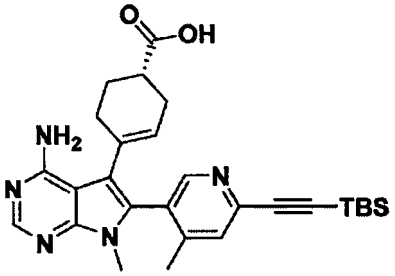
[1768] 流程30

[1769]



[1770] (S)-4-(4-氨基-6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-甲酸

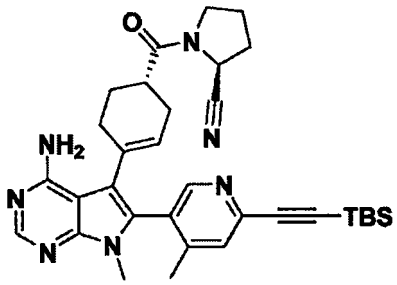
[1771]



[1772] 步骤1:向圆底烧瓶中装入(1S)-4-{4-氨基-6-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}环己-3-烯-1-甲酸(6g,19.5mmol)、{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}硼酸(10.7g,39.0mmol)、Na2CO3(6.19g,58.4mmol)、Xphos Pd.G3.(1.65g,1.95mmol)、Xphos(928mg,1.95mmol)、二恶烷/H2O(120mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物1小时。过滤反应混合物,用DCM洗涤,真空浓缩滤液,且所得粗物质然后通过combiflash(A:0.1%TFA/水,B:乙腈)来纯化。真空浓缩,产生呈黄色固体状的(1S)-4-(4-氨基-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-甲酸(6.20g,63%)。

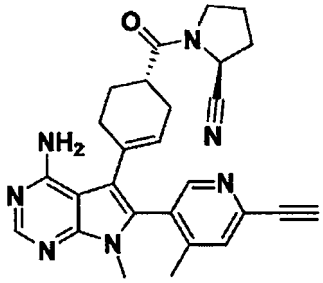
[1773] (S)-1-((S)-4-(4-氨基-6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-

基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈

[1774] 

[1775] 步骤2:向圆底烧瓶中装入(1S)-4-(4-氨基-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-甲酸(5g,9.96mmol)、(2S)-吡咯烷-2-甲腈(2.86g,29.8mmol)、HATU(7.56g,19.9mmol)、DMF(100mL)及搅拌棒。添加DIEA(15.0g,116mmol),且在室温下搅拌溶液2小时。反应混合物用水(150mL)稀释,且水相用EA(300mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(200g柱;用二氯甲烷/甲醇洗脱;比率=30:1)。真空浓缩,产生呈深色油状的(2S)-1-[(1S)-4-(4-氨基-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基]吡咯烷-2-甲腈(2.80g,48%)。

[1776] (S)-1-((S)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈

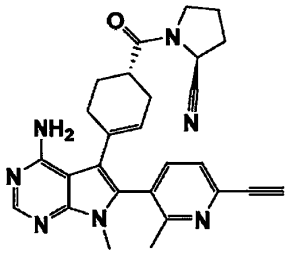
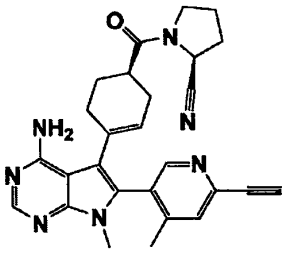
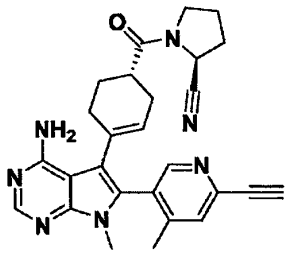
[1777] 

[1778] 步骤3:向圆底烧瓶中装入(2S)-1-[(1S)-4-(4-氨基-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基]吡咯烷-2-甲腈(2.7g,4.65mmol)、THF(10mL)及搅拌棒。添加TBAF(1.21g,4.65mmol),且在室温下搅拌溶液30分钟。反应混合物用水(150mL)稀释,且水相用DCM(100mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过flash(移动相A:水,移动相B:ACN)来纯化。所得粗物质通过HPLC纯化(柱:Xselect CSH OBD柱30*150mm 5um,n;移动相A:水(0.1%FA),移动相B:MeOH--HPLC;流量:60mL/min;梯度:20B至45B,历时7分钟;220nm:RT1:7.13;RT2)。冻干产生呈灰白色无定形固体状的(2S)-1-[(1S)-4-[4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-羰基]吡咯烷-2-甲腈(520mg,24%)。

[1779] 根据实例33的方法制备的其它化合物描绘于下表32中。

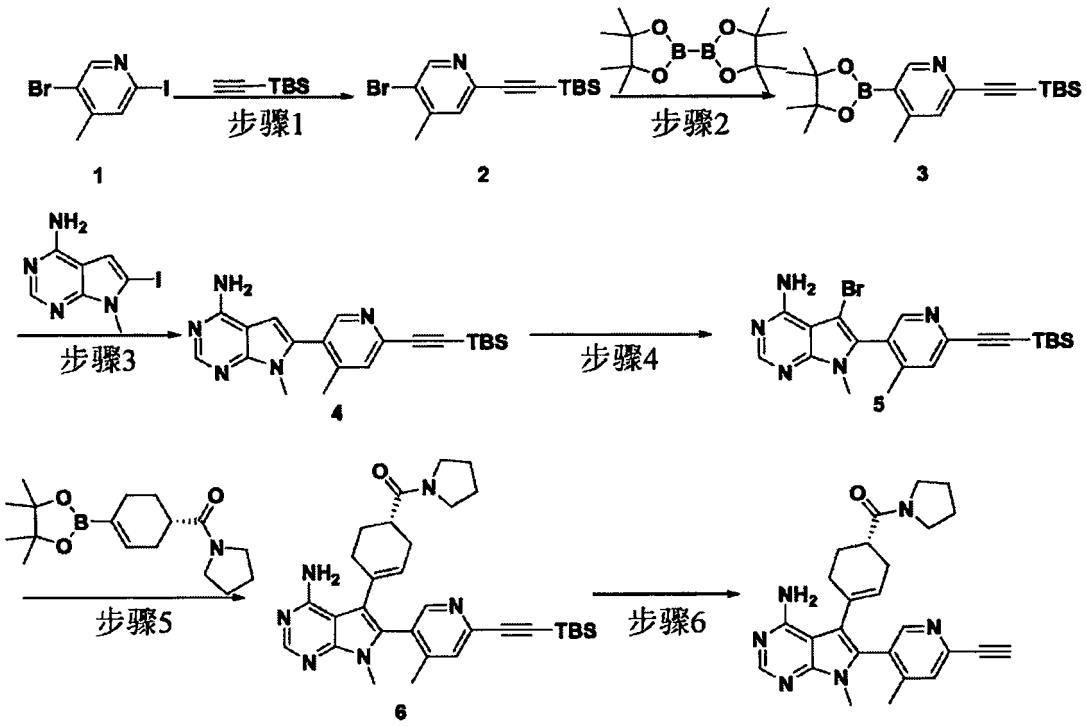
[1780] 表32.其它示例性化合物

[1781]

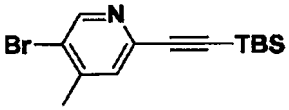
化合物	结构	质子 NMR	MS [M+1]
(2S)-1-[(1S)-4-[4-氨基-6-(6-乙炔基-2-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-羰基]吡咯烷-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.88 - 7.64 (m, 1H), 7.53 (d, J = 7.9 Hz, 1H), 6.57 (s, 1H), 5.70 (d, J = 11.1 Hz, 1H), 4.92 - 4.54 (m, 1H), 4.43 (s, 1H), 3.68 (d, J = 8.0 Hz, 1H), 3.53 - 3.43 (m, 1H), 3.38 (s, 3H), 2.81 (d, J = 6.4 Hz, 1H), 2.28 (d, J = 2.3 Hz, 3H), 2.23 (s, 2H), 2.13 (d, J = 6.5 Hz, 2H), 2.09 - 1.73 (m, 4H), 1.61 (s, 2H).	466.30
(2S)-1-[(1R)-4-[4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-羰基]吡咯烷-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 25.1 Hz, 1H), 8.17 (s, 1H), 7.64 (d, J = 3.9 Hz, 1H), 6.73 (s, 1H), 5.71 (d, J = 28.0 Hz, 1H), 4.71 (dd, J = 7.9, 3.8 Hz, 1H), 4.43 (s, 1H), 3.70 - 3.48 (m, 2H), 3.39 (d, J = 1.5 Hz, 3H), 2.86 - 2.74 (m, 1H), 2.28 - 2.20 (m, 2H), 2.14 (d, J = 7.2 Hz, 5H), 2.06 - 1.83 (m, 4H), 1.72 - 1.58 (m, 2H).	466.20
(2S)-1-[(1S)-4-[4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-羰基]吡咯烷-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 5.1 Hz, 1H), 8.14 (s, 1H), 7.64 (d, J = 1.9 Hz, 1H), 6.53 (s, 1H), 5.76 (s, 1H), 4.70 (dt, J = 7.3, 3.2 Hz, 1H), 4.43 (d, J = 1.2 Hz, 1H), 3.69 (s, 1H), 3.65 - 3.42 (m, 1H), 3.38 (d, J = 0.9 Hz, 3H), 2.80 (s, 1H), 2.24 (s, 2H), 2.14 (s, 5H), 2.07 - 1.81 (m, 4H), 1.60 (s, 2H).	466.35

[1782] 实例34

[1783] 流程31

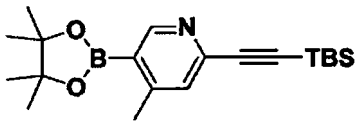
[1784] 

[1785] 5-溴-2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶

[1786] 

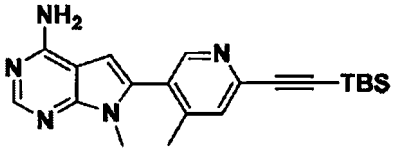
[1787] 步骤1:向可再密封的反应瓶中装入5-溴-2-碘-4-甲基吡啶(5.00g,16.8mmol)、二甲基甲酰胺(50mL)、CuI(1.28g,6.72mmol)、Et_3N(8.48g,84mmol)、$Pd(PPh_3)_2Cl_2$(2.36g,3.36mmol)、叔丁基(乙炔基)二甲基硅烷(2.35g,16.8mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。在50℃下搅拌混合物2小时。反应混合物用水(200mL)稀释,且水相用EA(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用庚烷/乙酸乙酯10:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的5-溴-2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶(4g,77%)。

[1788] 2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶

[1789] 

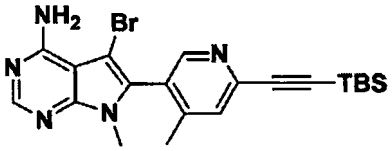
[1790] 步骤2:向可再密封的反应瓶中装入5-溴-2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶(3.5g,11.3mmol)、4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,3,2-二氧杂硼杂环戊烷(3.07g,12.1mmol)、AcOK(2.37g,24.2mmol)、$Pd(dppf)Cl_2$(589mg,807μmol)、二恶烷(40mL)及搅拌棒,随后抽真空且用氮气吹扫三次,且在80℃下搅拌混合物1小时。反应混合物用水(100mL)稀释,且水相用EA(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(乙腈/水0~50%)。冻干产生呈灰白色无定形固体状的2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(3.90g,90%)。

[1791] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1792] 

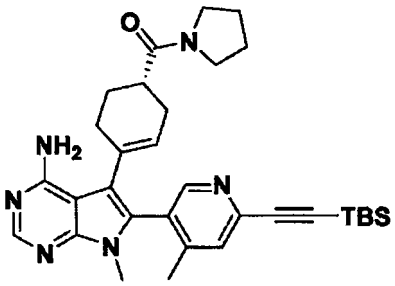
[1793] 步骤3:向可再密封的反应瓶中装入2-((叔丁基二甲基硅烷基)乙炔基)-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(2.6g 7.26mmol)、6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(1.67g,6.05mmol)、Pd(dppf)Cl_2(442mg,605μmol)、K_3PO_4(3.83g,18.1mmol)、DME:H_2O(10:1,25mL)及搅拌棒,随后抽真空且用氮气吹扫三次,且在90℃下搅拌混合物3小时。反应混合物用水(40mL)稀释,且水相用DCM(40mL)萃取三次。合并的有机层用饱和盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(乙腈/水=0~50%)。冻干产生呈黄色无定形固体状的6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-7-甲基-7H吡咯并[2,3-d]嘧啶-4-胺(1.6g,70%)。

[1794] 5-溴-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[1795] 

[1796] 步骤4:向圆底烧瓶中装入6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(1.6g,4.24mmol)、DCM(20mL)及搅拌棒。添加NBS(754.7mg,4.24mmol)。在室温下搅拌混合物1小时。反应混合物用饱和$NaHSO_3$水溶液淬灭直至pH至8-9,用DCM(100mL*3)萃取,合并有机相且用盐水洗涤,经Na_2SO_4干燥,真空蒸发,用ACN(25mL)溶解残余物,且过滤,用ACN洗涤滤饼,在减压下干燥,得到呈灰白色固体状的5-溴-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(1.6g,83%)。

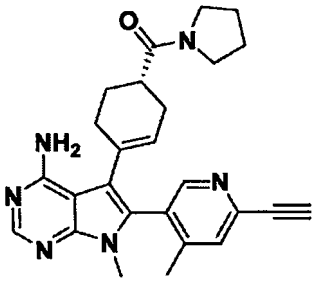
[1797] (S)-(4-(4-氨基-6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮

[1798] 

[1799] 步骤5:向可再密封的反应瓶中装入5-溴-6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(500mg,1.09mmol)、DME:H_2O(10:1,8mL)、[(4S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]硼酸(290mg,1.30mmol)、Pd(dppf)Cl_2(79.6mg,109μmol)、K_3PO_4(693mg,3.27mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物2小时。反应混合物用水(50mL)稀释,且水相用EA(30mL)萃取三

次。合并的有机层用饱和盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(1g柱;用EA洗脱)。真空浓缩,产生呈棕色固体状的6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-5-[(4S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(110mg,18%)。

[1800] (S)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮

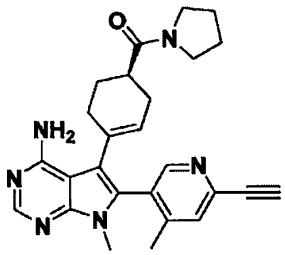
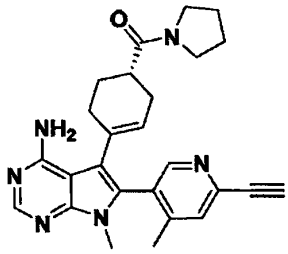
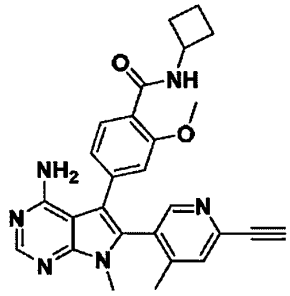
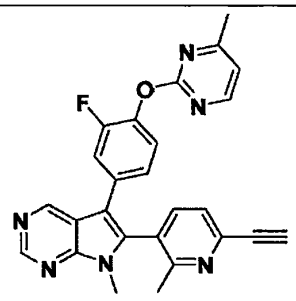
[1801] 

[1802] 步骤6:向可再密封的反应瓶中装入6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-7-甲基-5-[(4S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(100mg,180μmol)、THF(6mL)及搅拌棒。添加TBAF(2.2mL,216μmol),且在室温下搅拌混合物30分钟。反应混合物用水(20mL)稀释,且水相用DCM(20mL)萃取三次。合并的有机层用盐水洗涤五次,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型HPLC纯化(乙腈/水/10mmol NH_4HCO_3,流量:60mL/min;梯度:40B至65B,历时8分钟)。冻干产生呈灰白色无定形固体状的6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-[(4S)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(27.6mg,35%)。

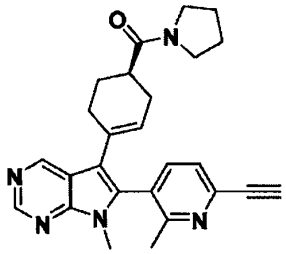
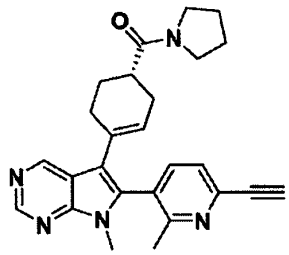
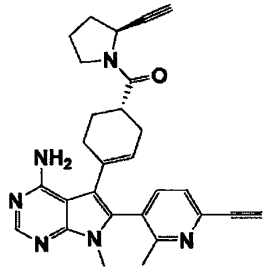
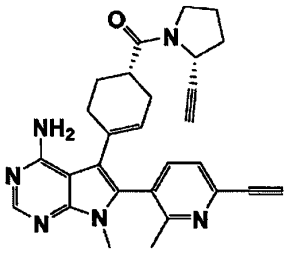
[1803] 根据实例34的方法制备的其它化合物描绘于下表33中。

[1804] 表33.其它示例性化合物

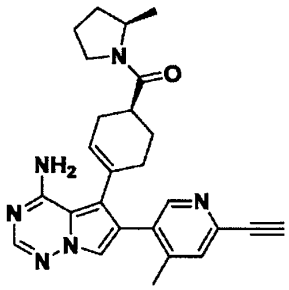
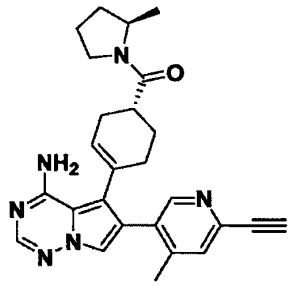
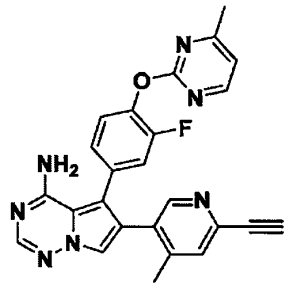
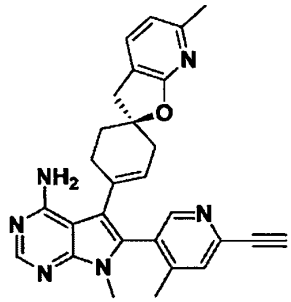
[1805]

化合物	结构	质子 NMR	MS [M+1]
(R)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) 8.40 (d, J = 11.7 Hz, 1H), 8.13 (s, 1H), 7.63 (d, J = 2.7 Hz, 1H), 6.59 (s, 1H), 5.69 (d, J = 30.0 Hz, 1H), 4.42 (d, J = 1.1 Hz, 1H), 3.51-3.38 (m, 2H), 3.37 (d, J = 1.4 Hz, 3H), 3.28 (s, 2H), 2.75 (s, 1H), 2.68 (p, J = 1.8 Hz, 2H), 2.34 (p, J = 1.9 Hz, 5H), 2.20 (d, J = 7.1 Hz, 1H), 1.93 (d, J = 9.1 Hz, 2H), 1.85 (q, J = 6.1 Hz, 2H), 1.60 (d, J = 7.0 Hz, 2H).	441.35
(S)-(4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.39 (d, J = 6.7 Hz, 1H), 8.17 (s, 1H), 7.65 (d, J = 3.2 Hz, 1H), 5.99 - 5.76 (m, 1H), 3.89 (d, J = 1.8 Hz, 1H), 3.62 - 3.50 (m, 2H), 3.49 (s, 3H), 3.43 (ddt, J = 9.3, 6.4, 3.7 Hz, 2H), 2.90 - 2.78 (m, 1H), 2.44 - 2.30 (m, 1H), 2.24 (d, J = 3.1 Hz,4H), 2.11 (s, 2H), 1.98 (qd, J = 6.4, 2.1 Hz, 2H), 1.90 (td, J = 6.5, 1.4 Hz, 2H), 1.76 (dq, J = 14.4, 6.3 Hz, 2H).	441.35
4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-N-环丁基-2-甲氧基苯甲酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.45 (s, 1H), 8.27 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 7.00 - 6.89 (m, 2H), 4.48 (p, J = 8.3 Hz, 1H), 3.86 (s, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 2.38 (d, J = 8.2 Hz, 2H), 2.13 - 1.99 (m, 5H), 1.85 - 1.75 (m, 2H).	467.15
6-(6-乙炔基-2-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO) 9.22 (s, 1H), 8.95 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.38 -7.23 (m, 2H), 7.17 (d, J = 5.1 Hz, 1H), 7.07 (ddd, J = 8.4, 2.2, 0.8 Hz, 1H), 4.47 (s, 1H), 3.57 (s, 3H), 2.40 (s, 3H), 2.14 (s, 3H).	451.15

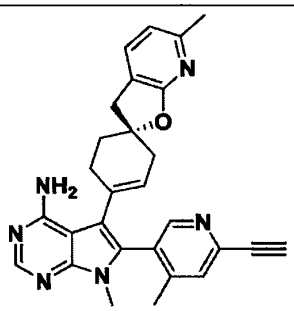
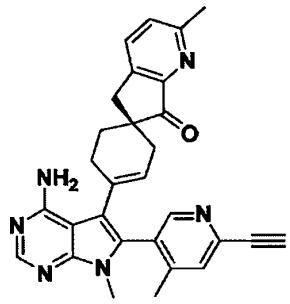
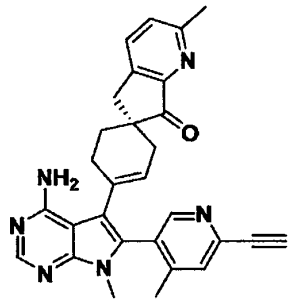
[1806]

化合物	结构	质子 NMR	MS [M+1]
(R)-(4-(6-(6-乙炔基-2-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) 9.14 (s, 1H), 8.86 (s, 1H), 7.86 (dd, J = 20.9, 7.9 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 5.81 (s, 1H), 4.47 (d, J = 1.7 Hz, 1H), 3.51 - 3.42 (m, 5H), 3.27 (t, J = 6.8 Hz, 2H), 2.61 (d, J = 12.8 Hz, 1H), 2.26 (t, J = 14.0 Hz, 7H), 1.87 (p, J = 6.7 Hz, 2H), 1.78 - 1.73 (m, 3H), 1.50 (td, J = 12.1, 5.7 Hz, 1H).	426.30
(S)-(4-(6-(6-乙炔基-2-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-基)(吡咯烷-1-基)甲酮		1H NMR (400 MHz, DMSO-d6) 9.14 (s, 1H), 8.86 (s, 1H), 7.86 (dd, J = 20.9, 7.9 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 5.81 (s, 1H), 4.46 (d, J = 1.7 Hz, 1H), 3.47 (dd, J = 6.8, 4.7 Hz, 5H), 3.30 (s, 2H), 2.61 (d, J = 11.0 Hz, 1H), 2.28 (d, J = 7.5 Hz, 3H), 2.23 (s, 2H), 2.18 (s, 1H), 1.91 - 1.83 (m, 2H), 1.85 -1.72 (m, 4H), 1.50 (td, J = 11.9, 5.5 Hz, 1H).	426.30
6-(6-乙炔基-2-甲基吡啶-3-基)-5-[(4S)-4-(2-乙炔基吡咯烷-1-羰基)环己-1-烯-1-基]-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 2.6 Hz, 1H), 7.73 (td, J = 6.7, 5.6, 2.4 Hz, 1H), 7.51 (s, 1H), 6.53 (s, 2H), 5.74 - 5.64 (m, 1H), 4.83 (d, J = 7.3 Hz, 1H), 4.43 (s, 1H), 3.61 (s, 1H), 3.38 (s, 3H), 3.26 (d, J = 11.8 Hz, 1H), 3.08 (d, J = 2.0 Hz, 1H), 2.96 - 2.63 (m, 1H), 2.32 - 2.15 (m, 3H), 2.15 - 2.06 (m, 2H), 2.04 - 1.80 (m, 6H), 1.75 - 1.53 (m, 2H).	465.30
6-(6-乙炔基-2-甲基吡啶-3-基)-5-[(4S)-4-[(2R)-2-乙炔基吡咯烷-1-羰基]环己-1-烯-1-基]-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) δ 8.13 (d, J = 3.1 Hz, 1H), 7.80 - 7.66 (m, 1H), 7.52 (d, J = 7.8 Hz, 1H), 6.56 (s, 2H), 5.71 (dd, J = 24.3, 13.7 Hz, 1H), 4.87 - 4.52 (m, 1H), 4.43 (s, 1H), 3.57 - 3.48 (m, 1H), 3.38 (s, 3H), 3.30 - 3.19 (m, 1H), 3.11 - 2.99 (m, 1H), 2.97 - 2.60 (m, 1H), 2.38 - 2.31 (m, 3H), 2.18 (d, J = 46.6 Hz, 3H), 1.92 (dd, J = 39.2, 17.7 Hz, 6H), 1.61 (s, 2H).	465.30

[1807]

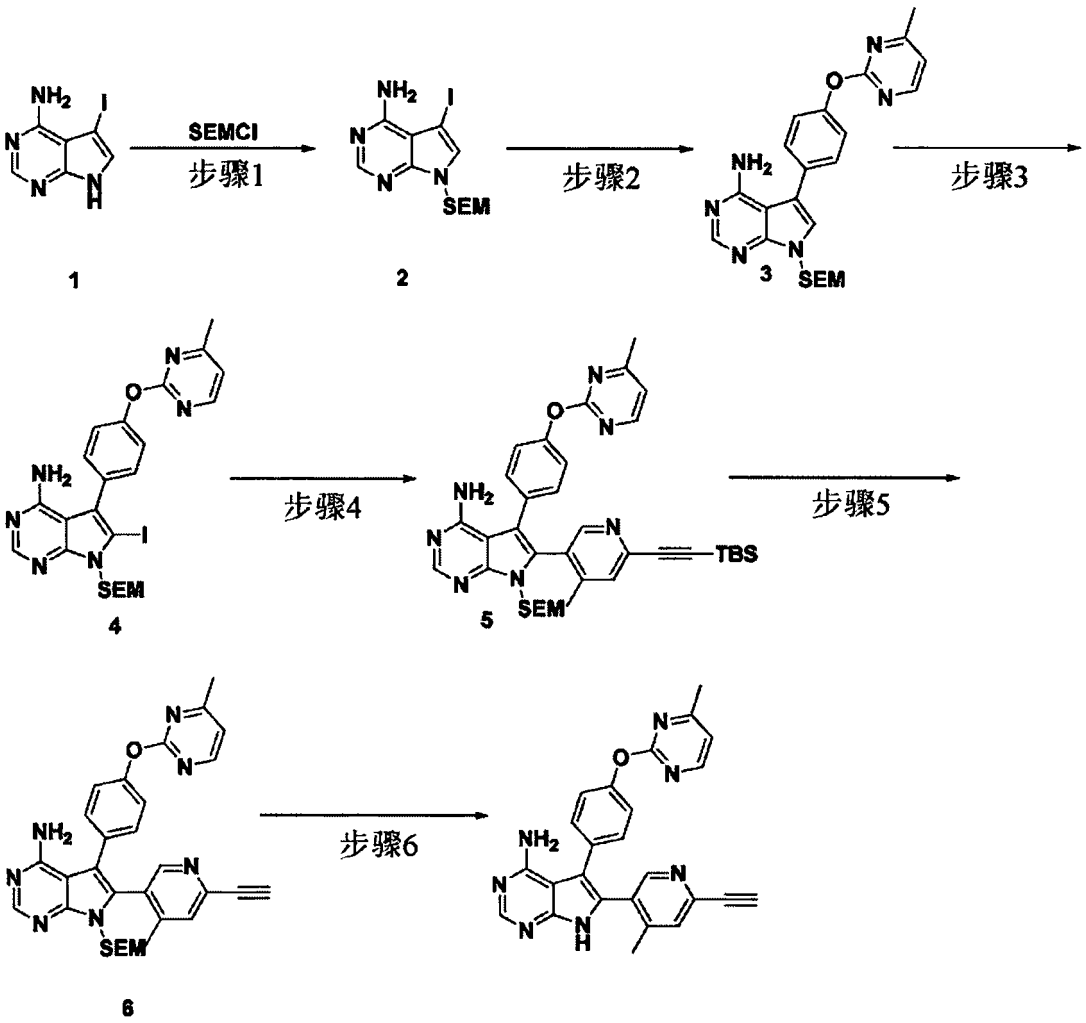
化合物	结构	质子 NMR	MS [M+1]
((S)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)吡咯并[2,1-f][1,2,4]三嗪-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.86 - 7.81 (m, 2H), 7.53 (d, J = 2.2 Hz, 1H), 6.88 (s, 1H), 5.83 (s, 1H), 4.32 (s, 1H), 4.00 (t, J = 6.5 Hz, 1H), 3.58 - 3.50 (m, 1H), 3.40 (s, 1H), 2.82 (t, J = 5.7 Hz, 1H), 2.27 (s, 5H), 1.99 - 1.72 (m, 5H), 1.66 - 1.38 (m, 3H), 1.09 (dd, J = 6.4, 2.0 Hz, 3H).	441.30
((R)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)吡咯并[2,1-f][1,2,4]三嗪-5-基)环己-3-烯-1-基)((R)-2-甲基吡咯烷-1-基)甲酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 1.9 Hz, 1H), 7.83 (d, J = 3.2 Hz, 2H), 7.52 (s, 1H), 7.20 (s, 1H), 5.86 (s, 1H), 4.32 (s, 1H), 4.08 - 3.93 (m, 1H), 3.50 (d, J = 7.6 Hz, 1H), 3.46 - 3.39 (m, 1H), 2.88 (s, 1H), 2.27 (s, 5H), 2.07 - 1.26 (m, 8H), 1.08 (dd, J = 38.2, 6.3 Hz, 3H).	441.30
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)吡咯并[2,1-f][1,2,4]三嗪-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.99 (d, J = 12.0 Hz, 2H), 7.45 (s, 1H), 7.37 (t, J = 8.3 Hz, 1H), 7.27 - 7.18 (m, 2H), 7.12 - 7.05 (m, 1H), 5.76 (s, 1H), 4.30 (s, 1H), 2.42 (s, 3H), 2.07 (s, 3H).	452.20
(R)-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-(6'-甲基-3'H-螺[环己烷-1,2'-呋喃并[2,3-b]吡啶]-3-烯-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 16.1 Hz, 1H), 8.17 (s, 1H), 7.66 (d, J = 5.6 Hz, 1H), 7.42 (dd, J = 7.3, 4.0 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 6.48 (d, J = 45.8 Hz, 2H), 5.64 (d, J = 52.5 Hz, 1H), 4.45 (d, J = 2.1 Hz, 1H), 3.49 - 3.37 (m, 3H), 2.98 - 2.62 (m, 2H), 2.30 (s, 6H), 2.17 (d, J = 4.3 Hz, 3H), 2.14 - 1.81 (m, 2H), 1.71 (ddd, J = 19.5, 12.6, 6.6 Hz, 1H).	463.20

[1808]

化合物	结构	质子 NMR	MS [M+1]
(S)-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-5-(6'-甲基-3'H-螺[环己烷-1,2'-呋喃并[2,3-b]吡啶]-3-烯-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 16.2 Hz, 1H), 8.18 (s, 1H), 7.66 (d, J = 5.6 Hz, 1H), 7.41 (dd, J = 7.3, 4.0 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 6.51 (s, 1H), 5.64 (d, J = 52.2 Hz, 1H), 4.44 (d, J = 2.0 Hz, 1H), 3.40 (s, 3H), 2.92 - 2.63 (m, 2H), 2.49 - 2.32 (m, 1H), 2.30 (s, 6H), 2.17 (d, J = 4.4 Hz, 3H), 2.13 - 1.81 (m, 2H), 1.70 (td, J = 12.5, 6.8 Hz, 1H).	463.25
(S)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2'-甲基螺[环己烷-1,6'-环戊并[b]吡啶]-3-烯-7'(5'H)-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 5.7 Hz, 1H), 8.16 (s, 1H), 7.85 (t, J = 8.6 Hz, 1H), 7.66 (d, J = 4.8 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 6.63 (s, 1H), 5.73 (d, J = 62.3 Hz, 1H), 4.45 (d, J = 2.7 Hz, 1H), 3.40 (d, J = 1.7 Hz, 3H), 2.89 - 2.58 (m, 2H), 2.55 (s, 3H), 2.44 - 2.28 (m, 1H), 2.17 (d, J = 2.3 Hz, 4H), 2.12 - 1.65 (m, 3H), 1.49 (dd, J = 17.5, 6.5 Hz, 1H).	475.25
(R)-4-(4-氨基-6-(6-乙炔基-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2'-甲基螺[环己烷-1,6'-环戊并[b]吡啶]-3-烯-7'(5'H)-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 5.4 Hz, 1H), 8.16 (s, 1H), 7.85 (t, J = 8.6 Hz, 1H), 7.67 (d, J = 4.8 Hz, 1H), 7.49 (dd, J = 8.1, 1.5 Hz, 1H), 6.58 (d, J = 31.4 Hz, 2H), 5.74 (d, J = 62.1 Hz, 1H), 4.45 (d, J = 2.7 Hz, 1H), 3.41 (d, J = 1.7 Hz, 3H), 2.93 - 2.58 (m, 2H), 2.55 (s, 3H), 2.43 - 2.31 (m, 1H), 2.17 (d, J = 2.3 Hz, 4H), 2.16 - 1.63 (m, 3H), 1.49 (dt, J = 11.4, 6.8 Hz, 1H).	475.30

[1809] 实例35

[1810] 流程32

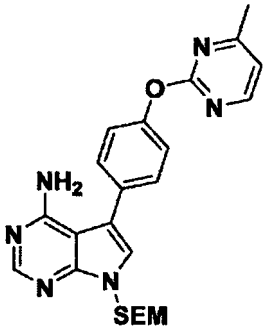
[1811] 

[1812] 5-碘-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1813]

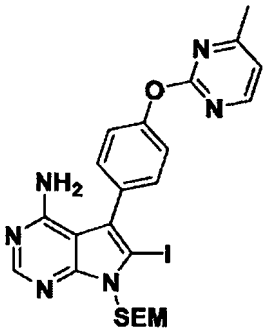
[1814] 步骤1:向圆底烧瓶中装入5-碘-7H-吡咯并[2,3-d]嘧啶-4-胺(2g,7.69mmol)、Cs_2CO_3(7.49g,23.0mmol)及搅拌棒。添加二甲基甲酰胺(40mL),且在0℃下搅拌溶液30分钟。然后添加[2-(氯甲氧基)乙基]三甲基硅烷(1.53g,9.22mmol)。反应混合物用H_2O(20mL)稀释,且水相用EA(100mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用二氯甲烷/甲醇洗脱;40/1-30/1)。真空浓缩,产生呈灰白色无定形固体状的5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.60g,53.2%)。

[1815] 5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1816] 

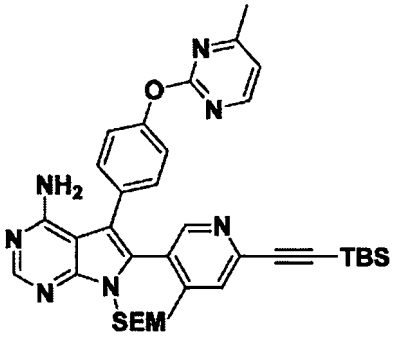
[1817] 步骤2:向可再密封的反应瓶中装入5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.6g,4.09mmol)、4-甲基-2-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]嘧啶双(甲烷)(1.54g,4.49mmol)、K_3PO_4(2.58g,12.2mmol)、DME/H_2O(16mL/2mL)、Pd(dppf)Cl_2(298mg,409μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌混合物1小时。反应混合物用H_2O(10mL)稀释,且水相用二氯甲烷(80mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用二氯甲烷/甲醇洗脱;20/1)。真空浓缩,产生呈橙色无定形固体状的5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.60g,87.0%)。

[1818] 6-碘-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]-甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺

[1819] 

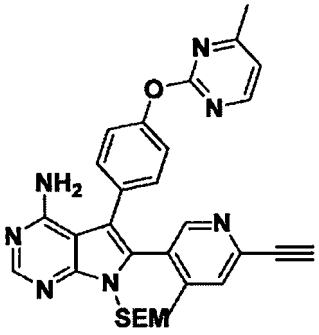
[1820] 步骤3:向圆底烧瓶中装入5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.6g,3.56mmol)、碘(硫基)胺(680mg,3.91mmol)、二氯甲烷(20mL)及搅拌棒,然后在0℃添加TFA(1.02g,10.6mmol)。在室温下搅拌混合物1小时。混合物用饱和$NaHSO_3$水溶液淬灭直至pH至8-9,用DCM(100mL)萃取三次,合并有机相且经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用二氯甲烷/甲醇洗脱;15/1)。真空浓缩,产生呈黄色无定形固体状的6-碘-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.40g,68.5%)。

[1821] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1822] 

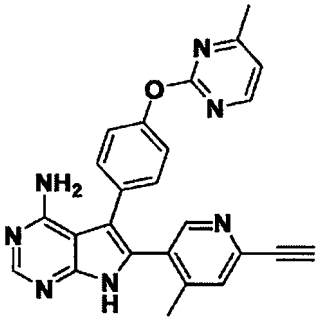
[1823] 步骤4:向可再密封的反应瓶中装入6-碘-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(400mg,696μmol)、2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)嘧啶(274mg,765μmol)、K_3PO_4(440mg,2.08mmol)、Pd(dppf)Cl_2(50.8mg,69.6μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(8mL/2mL),且在90℃下搅拌混合物1小时。反应混合物用H_2O(3mL)稀释,且水相用二氯甲烷(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(10g柱;用二氯甲烷/甲醇=15/1洗脱)。真空浓缩,产生呈黄色无定形固体状的6-{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基嘧啶-5-基}-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(310mg,65.5%)。

[1824] 6-(6-乙炔基-4-甲基吡啶-3-基)-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1825] 

[1826] 步骤5:向圆底烧瓶中装入6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(290mg,427μmol)、TBAF(133mg,512μmol)、THF(3mL)及搅拌棒,且在室温下搅拌溶液1小时。所得粗物质通过硅胶色谱纯化(20g柱;用二氯甲烷/甲醇15:1洗脱)。真空浓缩,产生呈黑色无定形固体状的6-(2-乙炔基-4-甲基嘧啶-5-基)-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(230mg,95.3%)。

[1827] 6-(6-乙炔基-4-甲基吡啶-3-基)-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

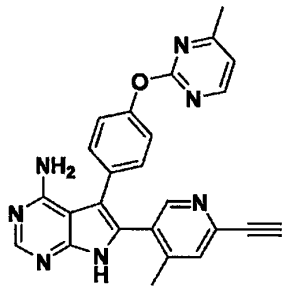
[1828] 

[1829] 步骤6:向圆底烧瓶中装入6-(6-乙炔基-4-甲基吡啶-3-基)-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(210mg,372μmol),及搅拌棒。添加TFA/DCM(40ml),且在室温下搅拌溶液30分钟。真空浓缩。添加MeOH/EDA(20ml),且在室温下搅拌溶液10分钟。真空浓缩。所得粗物质通过硅胶色谱纯化(5g柱;用二氯甲烷/甲醇洗脱;比率=20:1)。所得粗物质通过HPLC纯化(柱:YMC-Actus Triart C18,30*250,5um)。冻干产生呈灰白色无定形固体状的6-(6-乙炔基-4-甲基吡啶-3-基)-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(37.0mg,22.9%)。

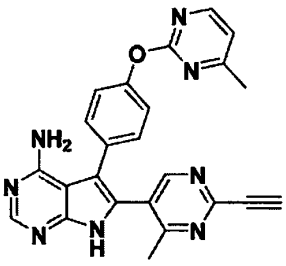
[1830] 根据实例35的方法制备的其它化合物描绘于下表34中。

[1831] 表34.其它示例性化合物

[1832]

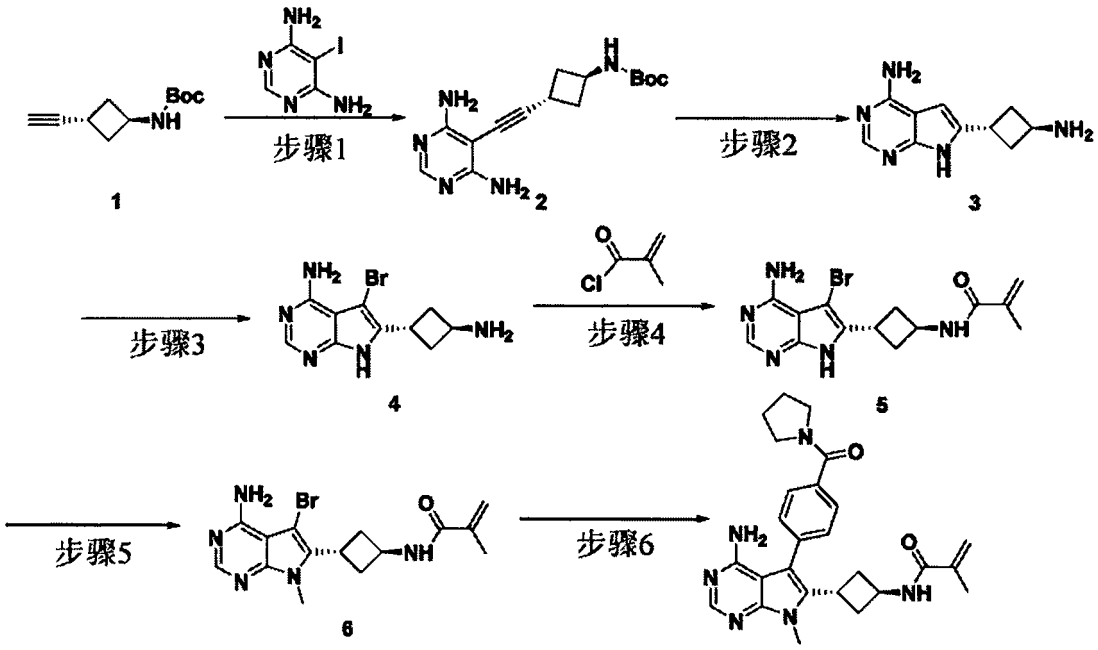
化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 7.51 (s, 1H), 7.31 - 7.24 (m, 2H), 7.24 - 7.18 (m, 2H), 7.16 (d, J = 5.0 Hz, 1H), 5.97 (s, 1H), 4.37 (s, 1H), 2.42 (s,3H), 2.08 (s, 3H).	434.25

[1833]

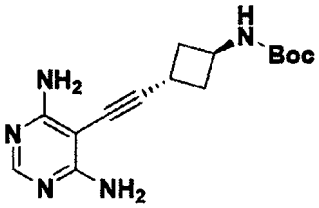
化合物	结构	质子 NMR	MS [M+1]
6-(2-乙炔基-4-甲基嘧啶-5-基)-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.20 (s, 1H), 7.31 (d, J = 8.2 Hz, 3H), 7.23 (d, J = 8.3 Hz, 4H), 7.16 (d, J = 5.1 Hz, 1H), 4.44 (s, 1H), 2.42 (s, 3H), 2.21 (s, 3H).	435.25

[1834] 实例36

[1835] 流程33

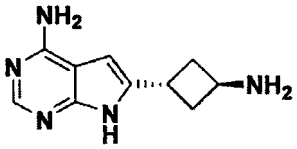
[1836] 

[1837] N-[(1r,3r)-3-[2-(4,6-二氨基嘧啶-5-基)乙炔基]环丁基]氨基甲酸叔丁酯

[1838] 

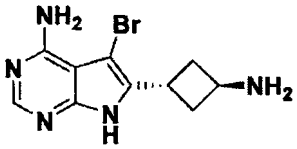
[1839] 步骤1:向5-碘嘧啶-4,6-二胺(1.00g,4.237mmol)及N-[(1r,3r)-3-乙炔基环丁基]氨基甲酸叔丁酯(0.99g,5.084mmol)于DMF(10mL)中的搅拌溶液中添加Pd(PPh3)2C12(297.40mg,0.424mmol)、CuI(161.39mg,0.847mmol)及TEA(1.29g,12.711mmol)。所得混合物在50℃下在氮气气氛下搅拌2小时。LCMS显示完成。残余物用CH_2Cl_2/MeOH(20:1)洗脱、通过硅胶柱色谱来纯化,得到呈棕色固体状的N-[(1r,3r)-3-[2-(4,6-二氨基嘧啶-5-基)乙炔基]环丁基]氨基甲酸叔丁酯(600mg,46.7%)。

[1840] 6-((1r,3r)-3-氨基环丁基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1841] 

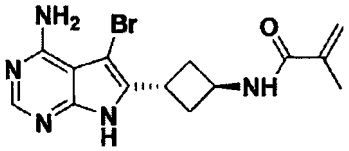
[1842] 步骤2:向N-[(1r,3r)-3-[2-(4,6-二氨基嘧啶-5-基)乙炔基]环丁基]氨基甲酸叔丁酯(600.00mg,1.978mmol)于NMP(10mL)中的搅拌溶液中添加叔丁醇钾(665.81mg,5.933mmol)。所得混合物在100℃下搅拌3小时。LCMS显示完成。残余物用CH_2Cl_2/MeOH(1:1)洗脱、通过硅胶柱色谱来纯化,得到呈棕色固体状的6-[(1r,3r)-3-氨基环丁基]-7H-吡咯并[2,3-d]嘧啶-4-胺(300mg,74.6%)。

[1843] 5-溴-6-[(1r,3r)-3-氨基环丁基]-7H-吡咯并[2,3-d]嘧啶-4-胺

[1844] 

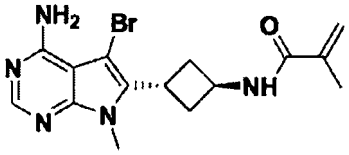
[1845] 步骤3:向6-[(1r,3r)-3-氨基环丁基]-7H-吡咯并[2,3-d]嘧啶-4-胺(300.00mg,1.476mmol)于DMF(5mL)中的搅拌溶液中添加NBS(262.71mg,1.476mmol)。所得混合物在0℃下搅拌1小时。LCMS显示完成。残余物用CH_2Cl_2/MeOH(1:1)洗脱、通过硅胶柱色谱来纯化,得到呈棕色固体状的5-溴-6-[(1r,3r)-3-氨基环丁基]-7H-吡咯并[2,3-d]嘧啶-4-胺(200mg,48%)。

[1846] N-((1r,3r)-3-(4-氨基-5-溴-7H-吡咯并[2,3-d]嘧啶-6-基)环丁基)甲基丙烯酰胺

[1847] 

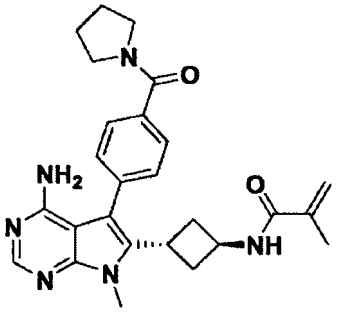
[1848] 步骤4:向5-溴-6-[(1r,3r)-3-氨基环丁基]-7H-吡咯并[2,3-d]嘧啶-4-胺(10.00mg,0.035mmol)及TEA(10.76mg,0.106mmol)于DCM(1mL)中的搅拌溶液中添加甲基丙烯酰氯(3.70mg,0.035mmol)。所得混合物在-30℃下搅拌1小时。反应混合物经由**Celite®**垫过滤,用DCM洗涤垫,且真空浓缩滤液。所得粗物质通过HPLC纯化(乙腈/水/0.1%甲酸)。冻干产生呈白色无定形固体状的N-((1r,3r)-3-(4-氨基-5-溴-7H-吡咯并[2,3-d]嘧啶-6-基)环丁基)甲基丙烯酰胺(3.00mg,24.5%)。

[1849] N-((1r,3r)-3-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)环丁基)甲基丙烯酰胺

[1850] 

[1851] 步骤5:向2-甲基-N-[(1r,3r)-3-[4-氨基-5-溴-7H-吡咯并[2,3-d]嘧啶-6-基]环丁基]丙-2-烯酰胺(60mg,0.171mmol)及Cs2CO3(167.46mg,0.514mmol)于DMF(2mL)中的搅拌溶液中添加CH3I(24.32mg,0.171mmol)。所得混合物在0℃下搅拌1小时。过滤所得混合物,用DMF洗涤滤饼。粗物质不经进一步纯化即直接用于下一步骤中。

[1852] N-((1r,3r)-3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丁基)甲基丙烯酰胺

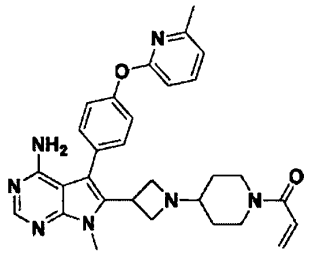
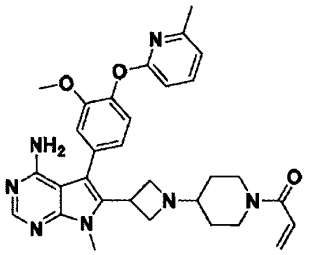
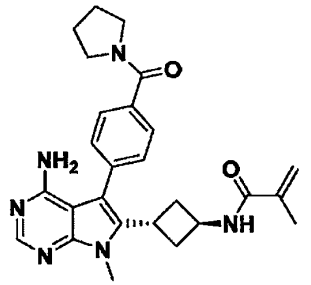
[1853] 

[1854] 步骤6:向2-甲基-N-[(1r,3r)-3-[4-氨基-5-溴-7-甲基吡咯并[2,3-d]嘧啶-6-基]环丁基]丙-2-烯酰胺(10.00mg,0.027mmol)及4-(吡咯烷-1-羰基)苯基硼酸(7.22mg,0.033mmol)于DMF(1mL)及水(0.1mL)中的溶液中添加CsF(12.51mg,0.082mmol)及Pd(DtBPF)Cl2(1.79mg,0.003mmol)。在90℃下在氮气气氛下搅拌残余物2小时。反应混合物用

水(10mL)稀释,且水相用二氯甲烷(10mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(5g柱;用二氯甲烷/甲醇/0.1%三乙胺洗脱;比率)。真空浓缩,产生呈白色无定形固体状的N-((1r,3r)-3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丁基)甲基丙烯酰胺(3.0mg,24.2%)。

[1855] 根据实例36的方法制备的其它化合物描绘于下表35中。

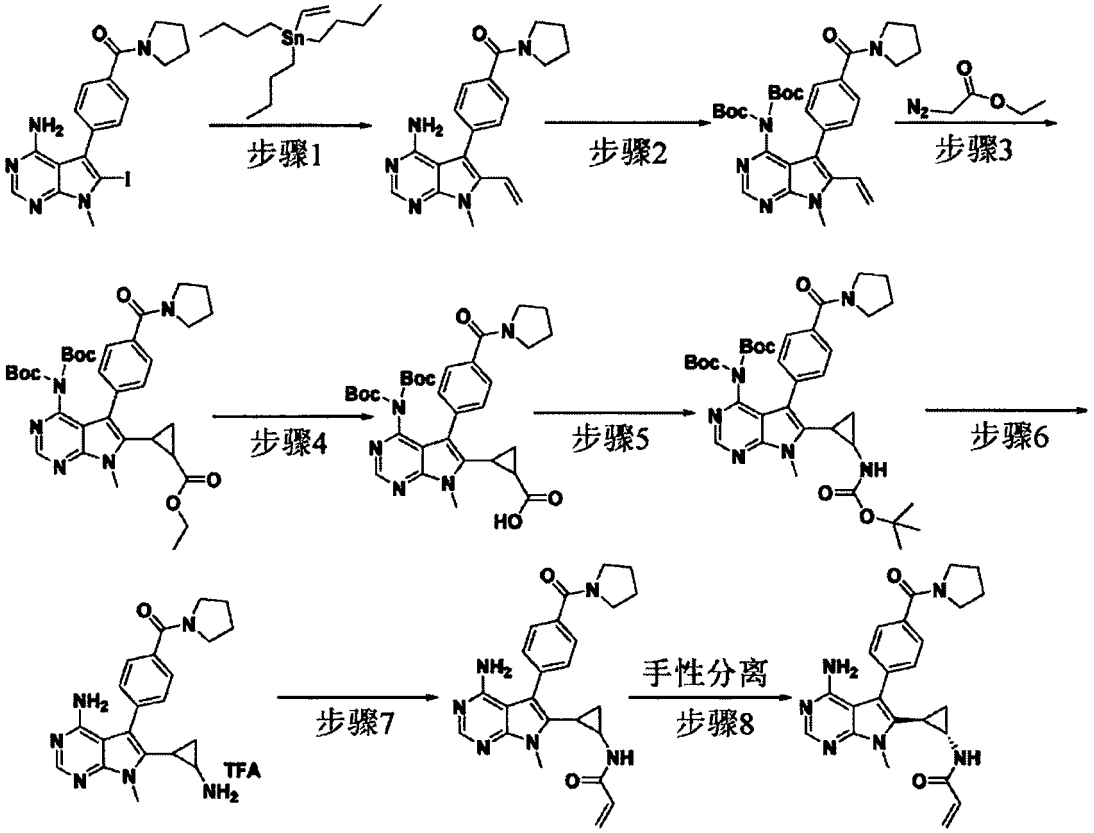
[1856] 表35.其它示例性化合物

化合物	结构	质子 NMR	MS [M+1]
1-(4-(3-(4-氨基-7-甲基-5-(4-(6-甲基吡啶-2-基氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)氮杂环丁-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.42 - 7.36 (m, 2H), 7.23 - 7.17 (m, 2H), 7.03 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.75 (dd, J = 16.7, 10.5 Hz, 1H), 6.05 (dd, J = 16.7, 2.4 Hz, 1H), 5.73 (s, 1H), 5.63 (dd, J = 10.5, 2.4 Hz, 1H), 3.99 (p, J = 8.0 Hz, 1H), 3.88 (d, J = 13.2 Hz, 1H), 3.75 (d, J = 13.4 Hz, 1H), 3.67 (s, 3H), 3.54 (t, J = 6.9 Hz, 2H), 3.15 (t, J = 11.5 Hz, 1H), 2.99 (t, J = 11.2 Hz, 1H), 2.77 (s, 2H), 2.35 (s, 3H), 2.07 (s, 1H), 1.48 (s, 2H), 1.03 (s, 2H).	523.64
1-(4-(3-(4-氨基-5-(3-甲氧基-4-(6-甲基吡啶-2-基氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)氮杂环丁-1-基)哌啶-1-基)丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 1.9 Hz, 1H), 7.00 - 6.92 (m, 2H), 6.76 (dd, J = 16.7, 10.5 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.05 (dd, J = 16.7, 2.4 Hz, 2H), 5.63 (dd, J = 10.5, 2.5 Hz, 1H), 4.03 (p, J = 8.1 Hz, 1H), 3.90 (d, J = 12.9 Hz, 1H), 3.69 (d, J = 14.5 Hz, 5H), 3.59 (s, 2H), 3.15 (s, 1H), 2.97 (d, J = 11.5 Hz, 1H), 2.81 (s, 2H), 2.30 (s, 3H), 2.09 (s, 1H), 1.50 (s, 2H), 1.04 (s, 2H).	553.66
N-((1r,3r)-3-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丁基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 6.4 Hz, 1H), 8.11 (s, 1H), 7.62 (d, J = 7.7 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 5.64 (s, 2H), 5.36 - 5.31 (m, 1H), 4.08 - 4.00 (m, 2H), 3.70 (s, 3H), 3.54 - 3.44 (m, 4H), 2.29 (t, J = 7.5 Hz, 4H), 1.88 (dt, J = 11.3, 5.7 Hz, 3H), 1.84 (s, 4H).	459.20

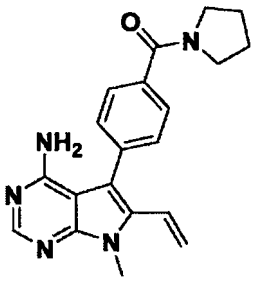
[1857]

[1858] 实例37

[1859] 流程34

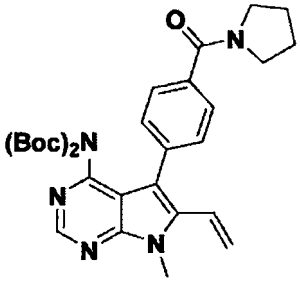
[1860] 

[1861] (4-(4-氨基-7-甲基-6-乙烯基-7H-吡咯并[2,3-d]嘧啶-5基)苯基)(吡咯烷-1-基)甲酮

[1862] 

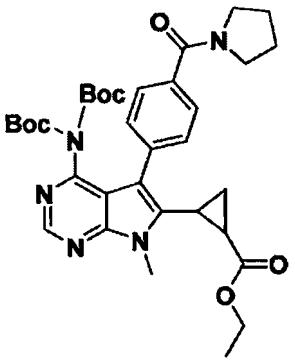
[1863] 步骤1:向可再密封的反应瓶中装入6-碘-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-胺(1g,2.23mmol)、三丁基(乙烯基)锡烷(846mg,2.67mmol)、Pd(PPh3)4(257mg,223μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二甲基甲酰胺(20mL),且在110℃下搅拌混合物整夜。反应混合物用水(50mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色无定形固体状的6-乙烯基-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-胺(700mg,90%)。

[1864] N-[(叔丁氧基)羰基]-N-{6-乙烯基-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-基}氨基甲酸叔丁酯

[1865] 

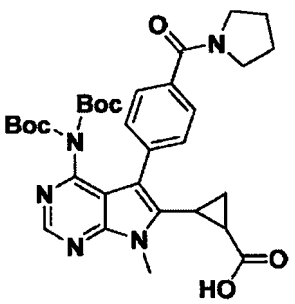
[1866] 步骤2:向圆底烧瓶中装入6-乙烯基-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-胺(700mg,2.01mmol)、二碳酸二-叔丁酯(1.75g,8.04mmol)、Et3N(813mg,8.04mmol)、DMAP(24.5mg,201μmol)、二氯甲烷(20mL)及搅拌棒。在室温下搅拌混合物整夜。反应混合物用水(50mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色无定形固体状的N-[(叔丁氧基)羰基]-N-{6-乙烯基-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-基}氨基甲酸叔丁酯(990mg,89%)。

[1867] 2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基)环丙烷-1-甲酸酯

[1868] 

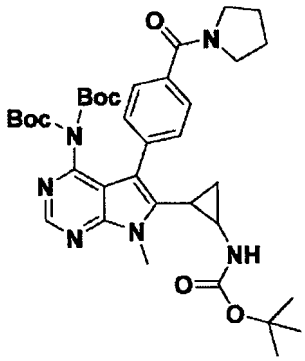
[1869] 步骤3:向可再密封的反应瓶中装入N-[(叔丁氧基)羰基]-N-{6-乙烯基-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-基}氨基甲酸叔丁酯(800mg,1.46mmol)、丙酸乙酯(149mg,1.46mmol)、5,10,15,20-四苯基-21H,23H-卟吩(19.6mg,29.2μmol)、甲苯(15mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在110℃下搅拌反应混合物2小时。反应混合物经由Celite®垫过滤,用二氯甲烷洗涤垫,且真空浓缩滤液。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色无定形固体状的2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3d]嘧啶-6-基)环丙烷-1-甲酸乙酯(550mg,59%)。

[1870] 2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基)环丙烷-1-甲酸

[1871] 

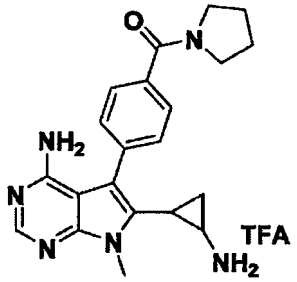
[1872] 步骤4:向圆底烧瓶中装入2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基)环丙烷-1-甲酸乙酯(1.7g,2.68mmol)、MeOH(15mL)及搅拌棒。添加NaOH水溶液(2M)(15mL),且在室温下搅拌溶液2小时。用HCl水溶液(2M)将pH调节至3～4,收集固体,真空干燥,产生呈灰白色固体状的2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基)环丙烷-1-甲酸(1.30g,80%)。

[1873] (叔丁氧基羰基)(6-(2-((叔丁氧基羰基)氨基)环丙基)-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-基)氨基甲酸叔丁酯

[1874] 

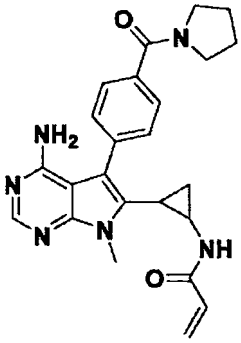
[1875] 步骤5:向圆底烧瓶中装入2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基)环丙烷-1-甲酸(400mg,660μmol)、TEA(73.3mg,726μmol)、DPPA(2.18g,7.92mmol)及搅拌棒。添加t-BuOH(10mL),且在80℃下搅拌溶液4小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过制备型HPLC(乙腈/水/0.1%甲酸)纯化。冻干产生呈灰白色无定形固体状的N-[2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基)环丙基]氨基甲酸叔丁酯(200mg,49%)。

[1876] (4-(4-氨基-6-(2-氨基环丙基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)苯基)(吡咯烷-1-基)甲酮

[1877] 

[1878] 步骤6:向圆底烧瓶中装入N-[2-(4-{双[(叔丁氧基)羰基]氨基}-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基)环丙基]氨基甲酸叔丁酯(200mg,295μmol)及搅拌棒。添加DCM:TFA=4:1(11mL),且在室温下搅拌溶液1小时。移除溶剂,粗产物(200mg)不经进一步纯化即直接用于下一步骤中。

[1879] N-(2-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丙基)丙烯酰胺

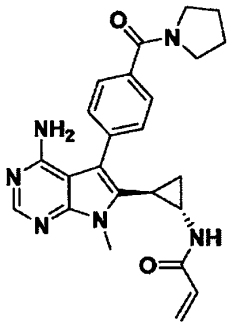
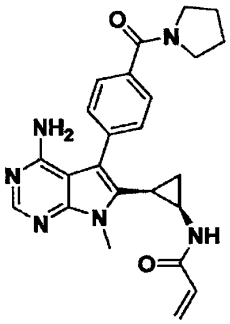
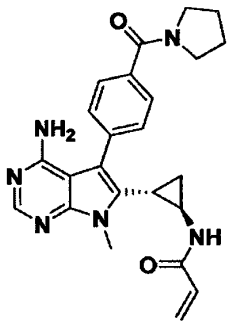
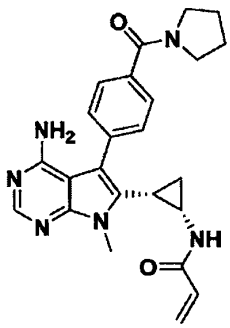
[1880] 

[1881] 步骤7:向圆底烧瓶中装入6-(2-氨基环丙基)-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-胺(200mg,0.42mmol)、TEA(213mg,2.1mmol)、二氯甲烷(10mL)及搅拌棒。在0℃下添加丙-2-烯酰氯(38mg,0.42mmol)。在0℃下搅拌反应混合物0.5小时。移除溶剂,所得粗物质通过制备型HPLC纯化(柱:XBridge Prep OBD C18柱,30×150mm 5um;移动相A:未定义,移动相B:未定义;流量:60mL/min;梯度:11B至35B,历时7分钟;254nm;RT1:6.75;RT2:;注射体积:ml;操作次数:;)。冻干产生呈灰白色无定形固体状的N-(2-{4-氨基-7-甲基-5-[4-(吡咯烷-1-羰基)苯基]-7H-吡咯并[2,3-d]嘧啶-6-基}环丙基)丙-2-烯酰胺(140mg,77%)。将物质送交手性分离(柱:CHIRALPAK IG,2*25cm,5um;移动相A:Hex:DCM=3:1(10mM NH3-MEOH)--HPLC,移动相B:EtOH--HPLC;流量:20mL/min;梯度:30B至30B,历时18分钟;220/254nm;RT1:7.758;RT2:10.625;注射体积:0.6ml;操作次数:10),产生四个峰:峰1(16.7mg)、峰2(28.5mg)、3(18.1mg)、峰4(28.8mg)。

[1882] 根据实例37的方法制备的其它化合物描绘于下表36中。

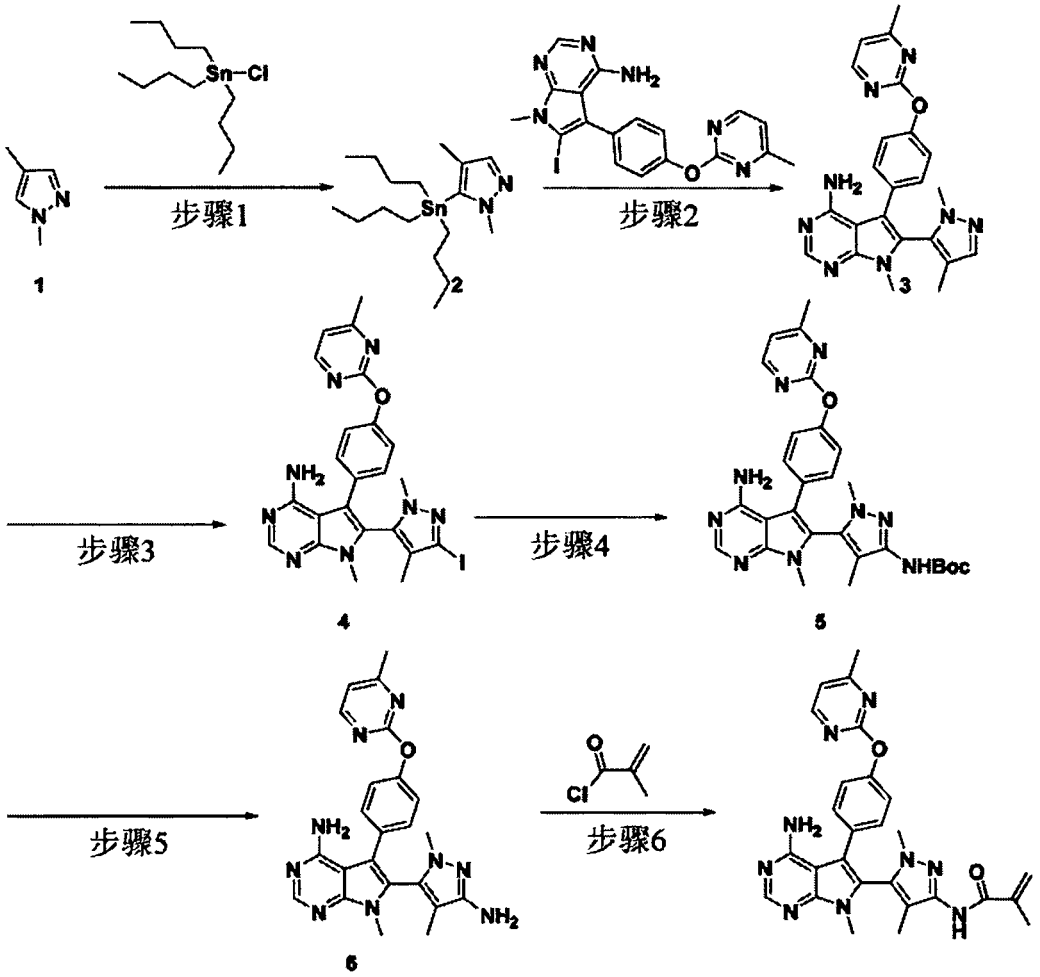
[1883] 表36.其它示例性化合物

[1884]

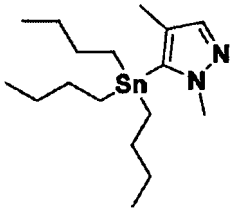
化合物	结构	质子 NMR	MS [M+1]
N-((1S,2S)-2-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丙基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.70 - 7.56 (m, 2H), 7.51 - 7.37 (m, 2H), 6.50 - 5.89 (m, 3H), 5.61 (dd, J = 9.6, 2.6 Hz, 1H), 3.89 (s, 3H), 3.49 (t, J = 6.9 Hz, 2H), 3.44 (q, J = 6.4 Hz, 2H), 2.70 (dq, J = 8.8, 4.5 Hz, 1H), 2.19 (ddd, J = 9.8, 6.4, 3.8 Hz, 1H), 1.87 (ddq, J = 25.5, 13.0, 6.7, 5.8 Hz, 4H), 1.01 (dt, J = 9.8, 5.1 Hz, 1H), 0.57 (dt, J = 7.6, 5.7 Hz, 1H).	431.20
N-((1R,2S)-2-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丙基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.70 (d, J = 6.5 Hz, 1H), 7.69 - 7.61 (m, 2H), 7.47 - 7.40 (m, 2H), 6.19 (s, 2H), 5.99 (d, J = 6.2 Hz, 2H), 5.48 (t, J = 6.2 Hz, 1H), 3.73 (s, 3H), 3.50 (td, J = 6.8, 3.0 Hz, 5H), 3.47 - 3.40 (m, 1H), 2.27 (dt, J = 9.1, 7.1 Hz, 1H), 1.88 (dp, J = 19.1, 6.7 Hz, 4H), 1.29 - 1.04 (m, 1H), 0.41 (q, J = 5.7 Hz, 1H).	431.20
N-((1R,2R)-2-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丙基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 7.67 - 7.53 (m, 2H), 7.49 - 7.40 (m, 2H), 6.45 - 5.98 (m, 3H), 5.61 (dd, J = 9.7, 2.7 Hz, 1H), 3.88 (s, 3H), 3.50 (d, J = 6.8 Hz, 2H), 3.49 - 3.40 (m, 2H), 2.70 (ddd, J = 8.7, 6.5, 3.1 Hz, 1H), 2.19 (ddd, J = 9.8, 6.4, 3.8 Hz, 1H), 1.89 (t, J = 6.6 Hz, 2H), 1.82 (q, J = 6.3 Hz, 2H), 1.01 (dt, J = 9.8, 5.2 Hz, 1H), 0.57 (dt, J = 7.6, 5.7 Hz, 1H).	431.20
N-((1S,2R)-2-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)环丙基)丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.69 (d, J = 6.5 Hz, 1H), 7.67 - 7.59 (m, 2H), 7.48 - 7.41 (m, 2H), 5.99 (d, J = 6.2 Hz, 3H), 5.47 (t, J = 6.2 Hz, 1H), 3.72 (s, 3H), 3.50 (td, J = 7.0, 3.5 Hz, 4H), 3.47 - 3.40 (m, 1H), 2.27 (dt, J = 9.1, 7.1 Hz, 1H), 1.88 (dp, J = 18.9, 6.8 Hz, 4H), 1.16 (td, J = 8.5, 5.8 Hz, 1H), 0.41 (dt, J = 7.1, 5.5 Hz, 1H).	431.20

[1885] 实例38

[1886] 流程35

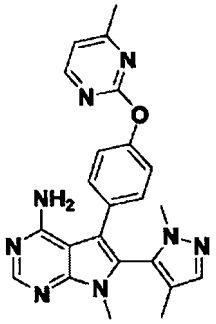
[1887] 

[1888] 1,4-二甲基-5-(三丁基锡烷基)-1H-吡唑

[1889] 

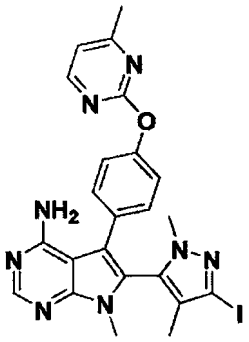
[1890] 步骤1:在-78℃下,在N2气氛下,向1,4-二甲基吡唑(2.00g,20.805mmol)于THF(15mL)中的溶液中逐滴添加正丁基锂溶液(2.5M,于THF中,1.07mL,16.644mmol)。在-78℃下搅拌反应混合物30分钟。然后逐滴添加Bu3SnCl(10.16g,31.207mmol)溶液且再搅拌混合物2小时。反应物用饱和NH4Cl(100mL)淬灭,且然后用EtOAc(3*50mL)萃取混合物。合并的有机萃取物用盐水(50mL)洗涤,经无水Na_2SO_4干燥,且在真空下浓缩,产生粗产物,通过硅胶柱色谱(PE/EA=4:1)来纯化,产生呈无色油状的1,4-二甲基-5-(三丁基锡烷基)吡唑(5.6g,69.9%)。

[1891] 6-(1,4-二甲基-1H-吡唑-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1892] 

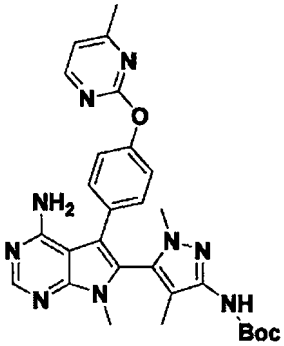
[1893] 步骤2:6-碘-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-4-胺(1.40g,3.055mmol)、1,4-二甲基-5-(三丁基锡烷基)吡唑(2.94g,7.638mmol)、肆(三苯膦)钯(353.03mg,0.306mmol)及碘化亚铜(I)(116.37mg,0.611mmol)于甲苯中的溶液/混合物在氮气气氛下、在110℃下搅拌整夜。反应混合物用水稀释,用CH_2Cl_2(3×50mL)萃取。合并的有机层用盐水(1x70mL)洗涤,经无水Na_2SO_4干燥。过滤之后,在减压下浓缩滤液。残余物用CH_2Cl_2/MeOH(12:1)洗脱、通过硅胶柱色谱来纯化,得到呈浅黄色固体状的6-(2,4-二甲基吡唑-3-基)-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-4-胺(320mg,24.6%)。

[1894] 6-(3-碘-1,4-二甲基-1H-吡唑-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1895] 

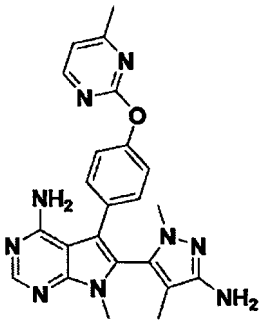
[1896] 步骤3:6-(3-碘-1,4-二甲基-1H-吡唑-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺(320mg,0.75mmol)、NIS(337mg,1.50mmol)及三氟乙醛(368mg,3.75mmol)于DCM中的溶液/混合物在60℃下搅拌48小时。反应混合物用水稀释,用CH_2Cl_2(3×30mL)萃取。合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,在减压下浓缩滤液。残余物通过制备型TLC(CH_2Cl_2/MeOH 10:1)纯化,得到呈淡黄色固体状的6-(3-碘-1,4-二甲基-1H-吡唑-5-基)-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-4-胺(171mg,41.3%)。

[1897] (5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基-1H-吡唑-3-基)氨基甲酸叔丁酯

[1898] 

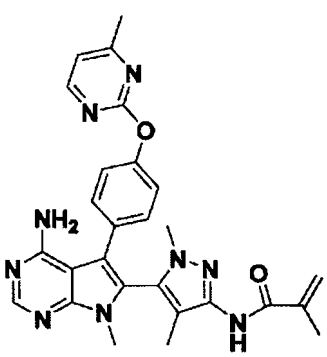
[1899] 步骤4:6-(5-碘-2,4-二甲基吡唑-3-基)-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-4-胺(170mg,0.31mmol)、氨基甲酸叔丁酯(72mg,0.62mmol)、碘化亚铜(I)(12mg,0.063mmol)及甲烷过氧酸钾(86mg,0.62mmol)于二恶烷中的溶液/混合物在氮气气氛下、在90℃下搅拌整夜。反应混合物用水稀释,用CH_2Cl_2(3×30mL)萃取。合并的有机层用盐水(1x30mL)洗涤,经无水Na_2SO_4干燥。过滤之后,在减压下浓缩滤液。通过制备型TLC(CH_2Cl_2/MeOH 10:1)来纯化残余物,得到呈无色油状的N-[5-(4-氨基-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基吡唑-3-基]氨基甲酸叔丁酯(25mg,15%)。

[1900] 6-(3-氨基-1,4-二甲基-1H-吡唑-5-基)-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[1901] 

[1902] 步骤5:N-[5-(4-氨基-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基吡唑-3-基]氨基甲酸叔丁酯(25mg,0.046mmol)于HCl(气体)/1,4-二恶烷(1mL)中的混合物在室温下搅拌10分钟。所得混合物在减压下浓缩。由此产生呈黄色油状的5-(4-氨基-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基吡唑-3-胺(25mg,98%)。

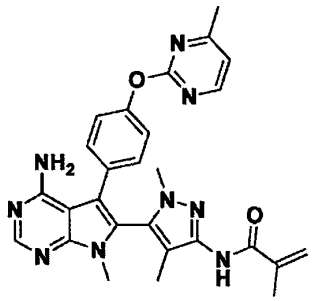
[1903] N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基-1H-吡唑-3-基)甲基丙烯酰胺

[1904] 

[1905] 步骤6:在0℃下向圆底烧瓶中装入5-(4-氨基-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基吡唑-3-胺(17mg,0.039mmol)、TEA(11.7mg,0.116mmol)于DCM(2mL)中,然后添加甲基丙烯酰氯(3.62mg,0.035mmol),搅拌2小时。所得粗物质通过制备型HPLC纯化(柱:XBridge制备型OBD C18柱,30×150mm 5um;移动相A:水(10MMOLLNH$_4$HCO$_3$),移动相B:ACN;流量:60mL/min;梯度:20B至45B,历时8分钟;220nm;RT1:5.78;RT2:;注射体积:ml;操作次数:;)。冻干产生呈灰白色无定形固体状的N-[5-(4-氨基-7-甲基-5-[4-[(4-甲基嘧啶-2-基)氧基]苯基]吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基吡唑-3-基]-2-甲基丙-2-烯酰胺(2.1mg,10.7%)。

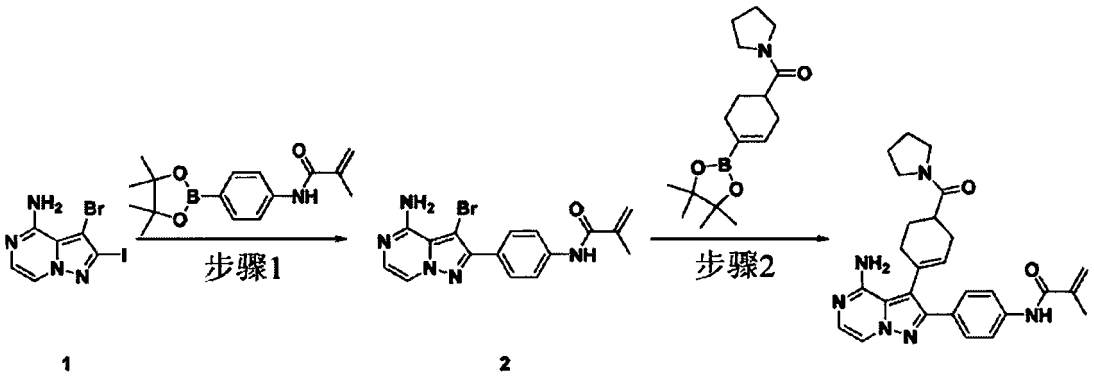
[1906] 表37.示例性化合物

[1907]

化合物	结构	质子 NMR	MS [M+1]
N-(5-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-1,4-二甲基-1H-吡唑-3-基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 氯仿-d) 8.44 (s, 1H), 8.39 (d, J = 5.0 Hz, 1H), 7.54 (s, 1H), 7.26 (q, J = 8.7 Hz, 4H), 6.95 (d, J = 5.0 Hz, 1H), 5.89 (s, 1H), 5.52 (s, 1H), 5.28 (s, 2H), 3.68 (s, 3H), 3.38 (s, 3H), 2.52 (s, 3H), 2.08 (s, 3H), 1.94 (s, 3H).	510.25

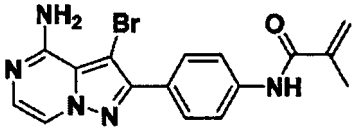
[1908] 实例39

[1909] 流程36

[1910] 

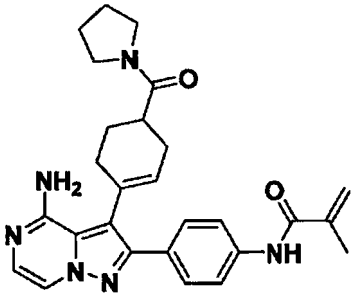
1 2

[1911] N-(4-(4-氨基-3-溴吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺

[1912] 

[1913] 向圆底烧瓶中装入3-溴-2-碘吡唑并[1,5-a]吡嗪-4-胺(1g,2.95mmol)、2-甲基-N-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]丙-2-烯酰胺(1.26g,4.42mmol)、Pd(dppf)C12(215mg,295μmol)、K3P04(1.87g,8.85mmol)、二恶烷(15mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌反应混合物1小时。反应混合物用水(50mL)稀释且用DCM(40mL*3)萃取,经无水硫酸钠干燥,过滤且真空蒸发。通过硅胶柱色谱来纯化残余物,得到呈灰白色无定形固体状的N-(4-(4-氨基-3-溴吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺(860mg,78.8%)。

[1914] N-(4-(4-氨基-3-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺

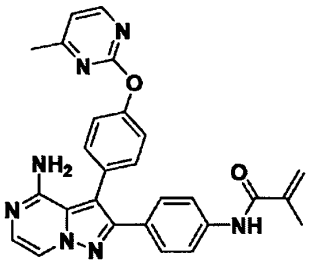
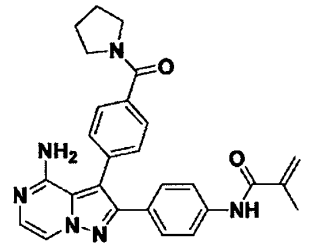
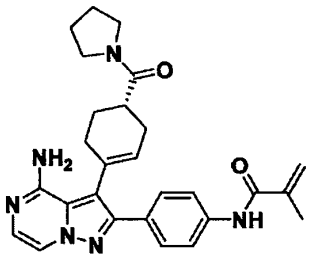
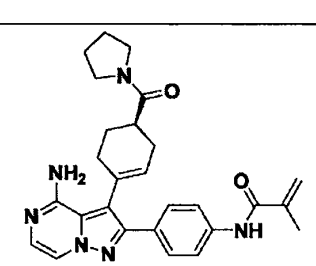
[1915] 

[1916] 向圆底烧瓶中装入N-(4-{4-氨基-3-溴吡唑并[1,5-a]吡嗪-2-基}苯基)-2-甲基丙-2-烯酰胺(100mg,268μmol)、1-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)环己-3-烯-1-羰基]吡咯烷(112mg,402μmol)、Pd(dtbpf)Cl2(17.4mg,26.8μmol)、CsF(122mg,804μmol)、DMF/H2O(10:1,5mL)及搅拌棒,随后抽真空且用氮气吹扫三次。在90℃下搅拌反应混合物1小时。反应混合物用水(20mL)稀释且用DCM(10mL*3)萃取。合并的有机相经无水硫酸钠干燥,过滤且蒸发。通过制备型HPLC纯化残余物(柱:Xselect CSH OBD柱30*150mm 5um,n;移动相A:水(0.1%FA),移动相B:ACN;流量:60mL/min;梯度:28B至60B,历时8分钟;220/254nm;RT1:6.55;RT2)。冻干产生呈白色无定形固体状的化合物(25mg,13%)。

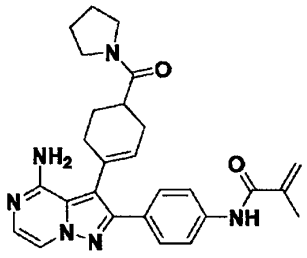
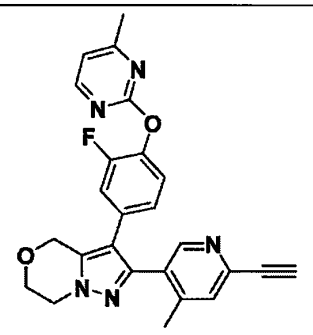
[1917] 根据实例39的方法制备的其它化合物描绘于下表38中。

[1918] 表38.其它示例性化合物

[1919]

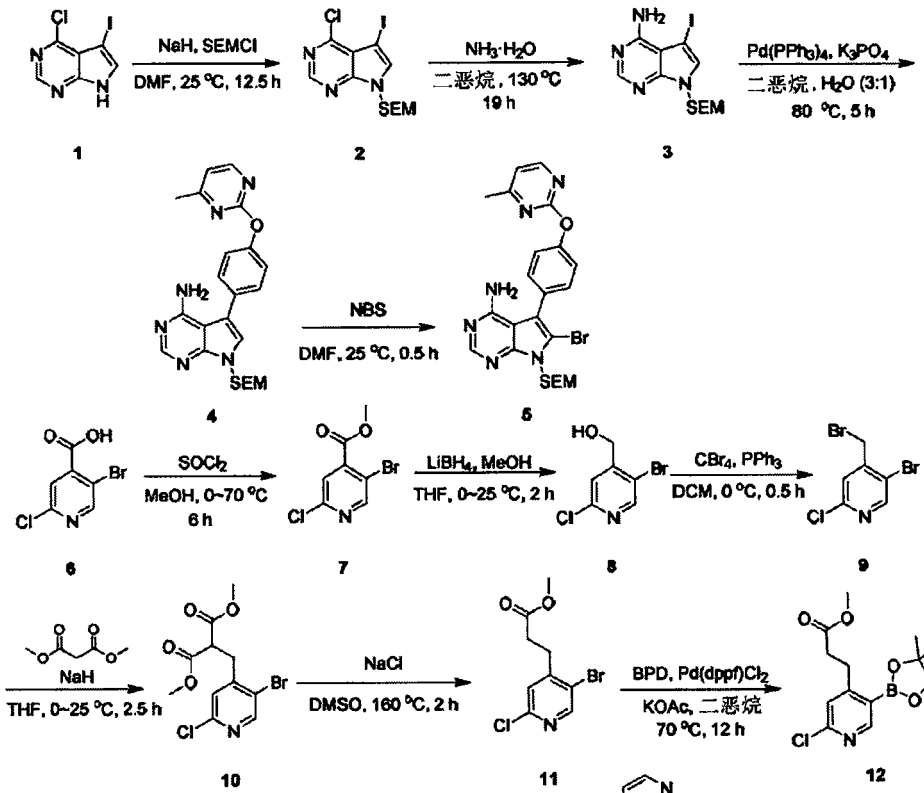
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-3-(4-((4-甲基嘧啶-2-基)氧基)苯基)吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d4) δ 8.46 (d, J = 5.0 Hz, 1H), 7.96 (d, J = 4.9 Hz, 1H), 7.63 - 7.56 (m, 2H), 7.55 - 7.45 (m, 4H), 7.38 - 7.30 (m, 2H), 7.30 (d, J = 4.9 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 5.83 - 5.78 (m, 1H), 5.55 - 5.50 (m, 1H), 2.53 (s, 3H), 2.04 (dd, J = 1.7, 0.9 Hz, 3H).	478.20
N-(4-(4-氨基-3-(4-(吡咯烷-1-羰基)苯基)吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, 甲醇-d_4) δ 7.97 (d, J = 4.8 Hz, 1H), 7.68 (d, J = 7.9 Hz, 2H), 7.55 (dd, J = 11.1, 8.2 Hz, 4H), 7.42 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 4.9 Hz, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 3.65 (t, J = 6.9 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 2.05 (d, J = 6.5 Hz, 1H), 2.03 (s, 4H), 1.97 (p, J = 6.9 Hz, 2H).	467.20
(S)-N-(4-(4-氨基-3-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.90 (d, J = 4.6 Hz, 1H), 7.77 (d, J = 2.7 Hz, 4H), 7.22 (d, J = 4.7 Hz, 1H), 6.74 (s, 2H), 5.95 (s, 1H), 5.83 (s, 1H), 5.54 (s, 1H), 3.63 - 3.53 (m, 1H), 3.49 (q, J = 8.7, 7.8 Hz, 1H), 3.39 (s, 1H), 3.36 (d, J = 5.0 Hz, 1H), 3.32 - 3.24 (m, 1H), 3.00 (s, 1H), 2.39 (s, 2H), 2.20 - 1.70 (m, 11H).	471.25
(R)-N-(4-(4-氨基-3-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.90 (d, J = 4.6 Hz, 1H), 7.77 (d, J = 2.7 Hz, 4H), 7.22 (d, J = 4.7 Hz, 1H), 6.74 (s, 2H), 5.95 (s, 1H), 5.83 (s, 1H), 5.54 (s, 1H), 3.63 - 3.53 (m, 1H), 3.49 (q, J = 8.7, 7.8 Hz, 1H), 3.39 (s, 1H), 3.36 (d, J = 5.0 Hz, 1H), 3.32 - 3.24 (m, 1H), 3.00 (s, 1H), 2.39 (s, 2H), 2.20 - 1.70 (m, 11H).	471.25

[1920]

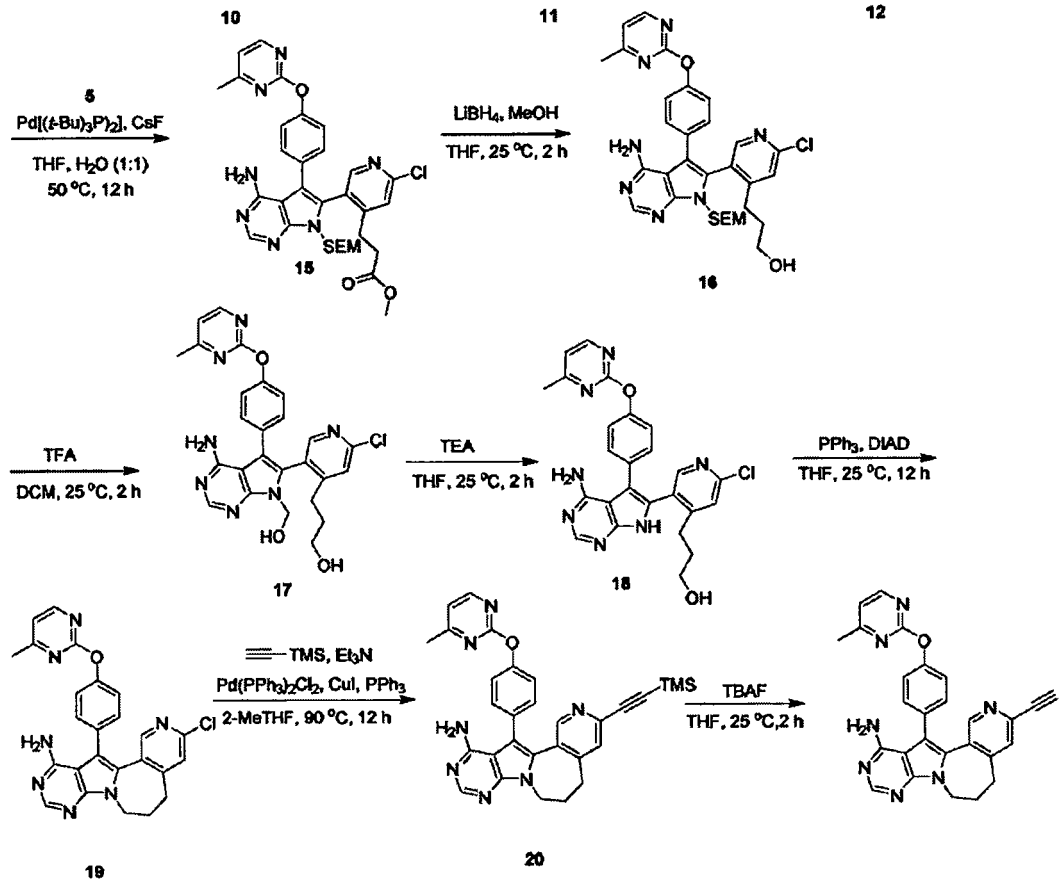
化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-3-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)吡唑并[1,5-a]吡嗪-2-基)苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.90 (d, J = 4.6 Hz, 1H), 7.77 (d, J = 2.7 Hz, 4H), 7.22 (d, J = 4.7 Hz, 1H), 6.74 (s, 2H), 5.95 (s, 1H), 5.83 (s, 1H), 5.54 (s, 1H), 3.63 - 3.53 (m, 1H), 3.49 (q, J = 8.7, 7.8 Hz, 1H), 3.39 (s, 1H), 3.36 (d, J = 5.0 Hz, 1H), 3.32 - 3.24 (m, 1H), 3.00 (s, 1H), 2.39 (s, 2H), 2.20 - 1.70 (m, 11H).	471.25
2-(6-乙炔基-4-甲基吡啶-3-基)-3-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-4H-吡唑并[5,1-c][1,4]恶嗪		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 5.0 Hz, 1H), 8.33 (s, 1H), 7.52 (d, J = 0.9 Hz, 1H), 7.29 (t, J = 8.4 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.02 (dd, J = 11.7, 2.1 Hz, 1H), 6.85 - 6.78 (m, 1H), 5.02 (s, 2H), 4.36 (s, 1H), 4.27 (t, J = 5.1 Hz, 2H), 4.17 (t, J = 5.2 Hz, 2H), 2.42 (s, 3H), 2.07 (s, 3H).	442.15

[1921] 实例40

[1922] 流程37



[1923]



[1924] 4-甲基-2-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]嘧啶

[1925] 步骤1:将t-BuOK(7.24g,2.0eq,77.6mmol)分数份添加2-氯-4-甲基嘧啶(5.00g,1.2eq,38.80mmol)及4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯酚(7.10g,32.30mmol)于DMF(30.0mL)中的溶液,且在120℃下搅拌溶液12小时。将反应混合物冷却且

用水(50.0mL)稀释,然后用EtOAc(30.0mL×3)萃取,在减压下浓缩合并的有机层。残余物通过柱色谱纯化(石油醚/EtOAc=10/1至4/1)。4-甲基-2-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]嘧啶(2.90g,22.9%产量)以混合物形式获得,其不经进一步纯化即用于下一步骤。

[1926] 4-氯-5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶

[1927] 步骤2:向4-氯-5-碘-7H-吡咯并[2,3-d]嘧啶(5.00g,17.80mmol)于DMF(20.0mL)中的溶液中添加NaH(1.06g,1.5eq,26.70mmol,60%纯度),所得混合物在25℃下搅拌0.5小时,然后添加SEMCl(3.85g,1.3eq,23.14mmol)。在25℃下搅拌反应混合物12小时。过滤反应混合物且在减压下浓缩。残余物通过柱色谱纯化(石油醚/EtOAc=10/1至4/1)。获得呈白色固体状的4-氯-5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(3.90g,53.4%产量)。

[1928] 5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺

[1929] 步骤3:4-氯-5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(3.90g,9.51mmol)于二恶烷(15.0mL)及$NH_3 \cdot H_2O$(15.0mL,15.8eq,150.26mmol,25%纯度)中的溶液在高压釜中、在130℃下搅拌19小时。冷却反应混合物且在减压下浓缩。残余物通过柱色谱纯化(石油醚/EtOAc=4/1至2/1)。获得呈白色固体状的5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(3.50g,94.3%产量)。

[1930] 5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺

[1931] 步骤4:5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(2.58g,6.62mmol)、4-甲基-2-(4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基)嘧啶(2.90g,1.4eq,9.27mmol)、$Pd(PPh_3)_4$(764.0mg,0.1eq,0.66mmol)、K_3PO_4(3.50g,2.5eq,16.55mmol)于二恶烷(30.0mL)及H_2O(10.0mL)中的溶液在80℃下搅拌5小时。冷却且过滤反应物,浓缩滤液,残余物通过柱色谱纯化(石油醚/EtOAc=1/1至0/1)。获得呈黄色油状的5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.70g,57.4%产率)。

[1932] 6-溴-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺

[1933] 步骤5:向5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.60g,3.56mmol)于DMF(30.0mL)中的溶液中分数份添加NBS(695.0mg,1.1eq,3.92mmol)。在25℃下搅拌反应物0.5小时。然后浓缩反应物且通过柱色谱纯化残余物(石油醚/EtOAc=4/1至2/1)。获得呈淡黄色固体状的产物6-溴-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(1.20g,64.1%产率)。

[1934] 5-溴-2-氯吡啶-4-甲酸甲酯

[1935] 步骤6:在0℃下,向5-溴-2-氯吡啶-4-甲酸(15.00g,63.40mmol)于MeOH(50.0mL)中的溶液中缓慢添加$SOCl_2$(11.30g,1.5eq,95.10mmol)。然后将反应混合物加热至70℃且在此温度下保持6小时。在减压下浓缩反应混合物,残余物通过柱色谱纯化(石油醚/EtOAc=10/1至5/1)。获得呈无色油状的5-溴-2-氯吡啶-4-甲酸甲酯(12.00g,75.9%产率)。

[1936] (5-溴-2-氯吡啶-4-基)甲醇

[1937] 步骤7:在0℃下,向5-溴-2-氯吡啶-4-甲酸甲酯(11.5g,45.90mmol)于THF(100.0mL)中的溶液中缓慢添加$LiBH_4$(1.49g,1.5eq,68.85mmol)。使所得溶液升温至25℃且在此温度下搅拌2小时,随后通过MeOH淬灭。在减压下浓缩反应混合物,残余物通过柱色谱(石油醚/EtOAc=10/1至3/1)纯化。获得呈白色固体状的(5-溴-2-氯吡啶-4-基)甲醇(6.70g,65.6%产率)。

[1938] 5-溴-4-(溴甲基)-2-氯吡啶

[1939] 步骤8:(5-溴-2-氯吡啶-4-基)甲醇(1.00g,4.49mmol)、PPh_3(1.76g,1.5eq,6.73mmol)及CBr_4(2.23g,1.5eq,6.73mmol)于DCM(15.0mL)中的溶液在0℃下搅拌0.5小时。在减压下浓缩反应混合物,残余物通过柱色谱纯化(石油醚/EtOAc=20/1至10/1)。获得呈无色油状的5-溴-4-(溴甲基)-2-氯吡啶(1.20g,93.7%产率)。

[1940] 2-[(5-溴-2-氯吡啶-4-基)甲基]丙二酸1,3-二甲酯

[1941] 步骤9:在0℃下,将NaH(1.07g,1.1eq,26.95mmol,60%纯度)悬浮于无水THF(70.0mL)中,且用丙二酸二甲酯(3.23g,1.0eq,24.50mmol)溶液逐滴处理。在25℃下搅拌30分钟之后,添加5-溴-4-(溴甲基)-2-氯吡啶(7.00g,24.50mmol)于无水THF(10.0mL)中的溶液且再继续搅拌2小时。反应混合物用水(1.0mL)淬灭且在减压下浓缩,残余物通过柱色谱纯化(石油醚/EtOAc=1/0至10/1)。获得呈白色固体状的2-[(5-溴-2-氯吡啶-4-基)甲基]丙二酸1,3-二甲酯(5.80g,70.3%产率)。

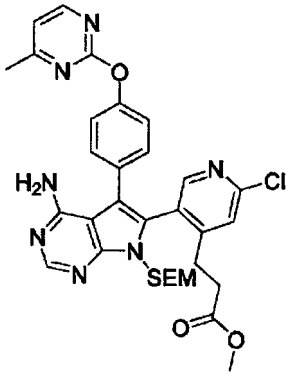
[1942] 3-(5-溴-2-氯吡啶-4-基)丙酸甲酯

[1943] 步骤10:2-[(5-溴-2-氯吡啶-4-基)甲基]丙二酸1,3-二甲酯(5.3g,15.70mmol)、NaCl(912.0mg,1.0eq,15.70mmol)及H_2O(563.0mg,2.0eq,31.40mmol)于DMSO(80.0mL)中的溶液在160℃下搅拌2小时。冷却至室温后,将反应混合物倾入EtOAc(70.0mL)中。所得溶液用H_2O(500.0mL)、盐水(300.0mL)洗涤,经无水$MgSO_4$干燥且然后在减压下浓缩,残余物通过柱色谱纯化(石油醚/EtOAc=20/1至10/1)。获得呈无色油状的3-(5-溴-2-氯吡啶-4-基)丙酸甲酯(2.60g,59.9%产率)。

[1944] 3-[2-氯-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-4-基]丙酸甲酯

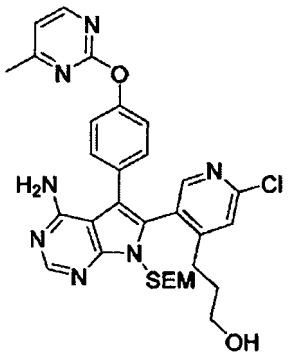
[1945] 步骤11:3-(5-溴-2-氯吡啶-4-基)丙酸甲酯(1.00g,3.59mmol)、BPD(1.09g,1.2eq,4.30mmol)、KOAc(1.05g,3.0eq,10.77mmol)及Pd(dppf)Cl_2(525.0mg,0.2eq,0.72mmol)于二恶烷(20.0mL)中的溶液在70℃下、在N_2下搅拌12小时。在减压下浓缩反应混合物,残余物通过柱色谱纯化(石油醚/EtOAc=20/1至10/1)。获得呈白色固体状的3-[2-氯-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-4-基]丙酸甲酯(0.90g,77.5%产率)。

[1946] 3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙酸甲酯

[1947] 

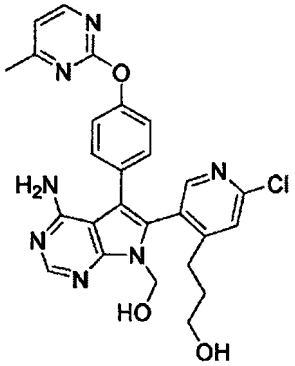
[1948] 步骤12:6-溴-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(550.0mg,1.04mmol)、3-[2-氯-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-4-基]丙酸甲酯(403.0mg,1.2eq,1.24mmol)、$Pd[Pd(t\text{-}Bu)_3]_2$(106.0mg,0.2eq,0.21mmol)及CsF(521.0mg,3.3eq,3.43mmol)于THF(20.0mL)及H_2O(20.0mL)中的溶液在50℃下、在N_2下搅拌12小时。在减压下浓缩反应混合物,残余物通过柱色谱纯化(MeOH/EtOAc=0/1至1/10)。获得呈棕色固体状的3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙酸甲酯(420.0mg,62.4%产率)。

[1949] 3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇

[1950] 

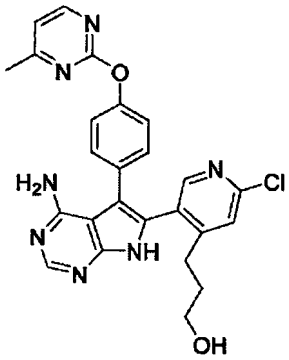
[1951] 步骤13:将$LiBH_4$(20.1mg,3.0eq,927.0mmol)缓慢添加至3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙酸甲酯(200.0mg,309.0μmol)于THF(15.0mL)及MeOH(24.7mg,2.0eq,618.0mmol)中的溶液中。反应混合物在25℃下搅拌2小时,随后通过MeOH(0.2mL)淬灭,浓缩反应混合物,残余物通过柱色谱纯化(DCM/MeOH=1/0至10/1)。获得呈白色固体状的3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(180.0mg,94.2%产率)。

[1952] 3-{5-[4-氨基-7-(羟基甲基)-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基]-2-氯吡啶-4-基}丙-1-醇

[1953] 

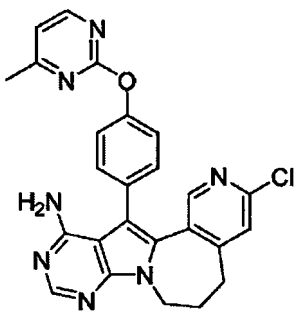
[1954] 步骤14:3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(190.0mg,307.0μmol)于DCM(15.0mL)及TFA(6.0mL)中的溶液在25℃下搅拌2小时。在减压下浓缩反应混合物。获得呈无色油状的3-{5-[4-氨基-7-(羟基甲基)-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基]-2-氯吡啶-4-基}丙-1-醇(155.0mg,97.4%产率),其不经进一步纯化即可用于下一步骤。

[1955] 3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇

[1956] 

[1957] 步骤15:3-{5-[4-氨基-7-(羟基甲基)-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基]-2-氯吡啶-4-基}丙-1-醇(155.0mg,299.0μmol)于THF(15.0mL)及TEA(6.0mL)中的溶液在25℃下搅拌2小时。浓缩反应物混合物,残余物通过柱色谱纯化(DCM/MeOH=1/0至10/1)。获得呈白色固体状的3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(120.0mg,82.7%产率)。

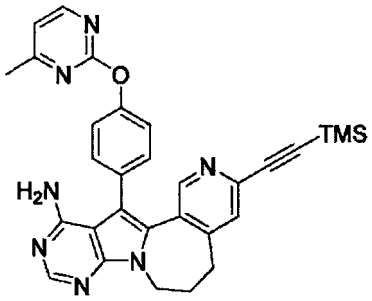
[1958] 3-氯-13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[1959] 

[1960] 步骤16:3-[5-(4-氨基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-

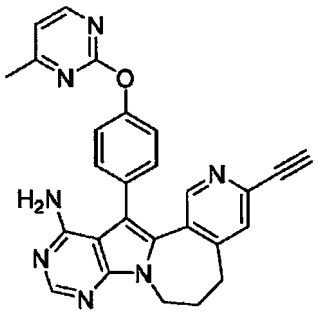
d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(180.0mg,368.0μmol)、PPh_3(193.0mg,2.0eq,736.0μmol)及DIAD(148.0mg,2.0eq,736.0μmol)于THF(5.0mL)中的溶液在25℃下、在N_2下搅拌12小时。浓缩反应混合物,残余物通过柱色谱纯化(DCM/MeOH=20/1至10/1)。获得呈白色固体状的3-氯-13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(90.0mg,52.3%产率)。

[1961] 13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三甲基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[1962] 

[1963] 步骤17:3-氯-13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(100.0mg,212.0μmol)、三甲基乙炔基硅(171.0mg,8.2eq,1.74mmol)、$Pd(PPh_3)_2Cl_2$(61.7mg,0.4eq,84.8μmol)、PPh_3(45.9mg,0.8eq,169.6μmol)、CuI(33.5mg,0.8eq,169.6μmol)及Et_3N(443.0mg,20.0eq,4.24mmol)于2-Me-THF(4.0mL)中的溶液在90℃下、在N_2下搅拌12小时。在减压下浓缩反应混合物,残余物通过柱色谱纯化(DCM/MeOH=10/0至10/1)。13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三甲基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(120.0mg,107%粗产率)以棕色混合物形式获得,其不经进一步纯化即可用于下一步骤。

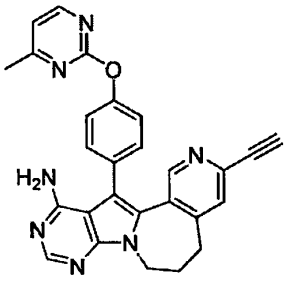
[1964] 3-乙炔基-13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[1965] 

[1966] 步骤18:向13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三甲基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(100.0mg,188.0μmol)于THF(20.0mL)中的溶液中添加TBAF于THF中的溶液(376.0μL,2.0eq,376.0mol)。所得混合物在25℃下搅拌2小时。在减压下浓缩反应混合物,残余物通过制备型HPLC纯化($NH_3 \cdot H_2O$)。获得呈白色固体状的3-乙炔基-13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(2.6mg,3.0%产率)。

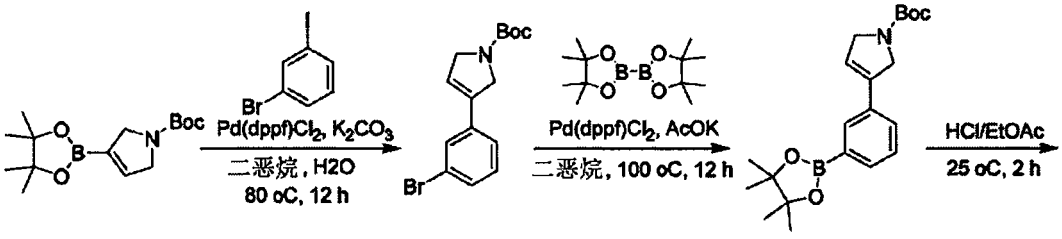
[1967] 表39.示例性化合物

[1968]

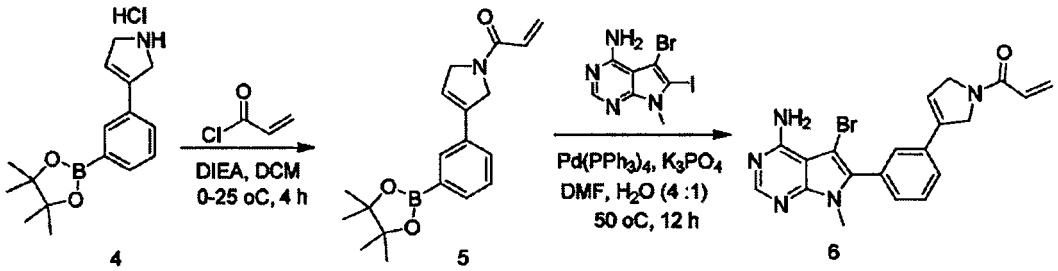
化合物	结构	质子 NMR	MS [M+1]
3-乙炔基-13-(4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5',4':4,5]吡咯并[1,2-a]氮呼-12-胺		^{1}HNMR (400 MHz, $CDCl_3$): δ 8.41-8.36 (m, 2H), 8.21 (s, 1H), 7.48 (s, 1H), 7.41-7.38 (m, 2H), 7.31-7.28 (m, 2H), 6.96 (s, 1H), 5.14 (s, 2H), 4.28 (m, 2H), 3.21 (s, 1H), 2.85-2.81 (m, 2H), 2.54 (s, 3H), 2.40-2.36 (m, 2H).	460.3

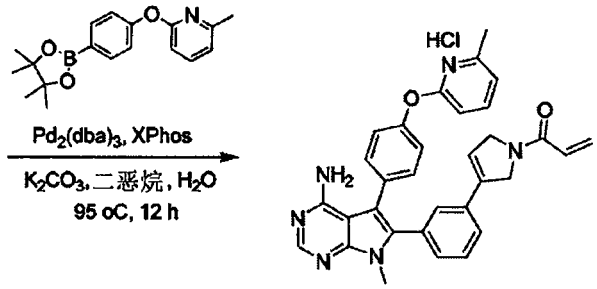
[1969] 实例41

[1970] 流程38



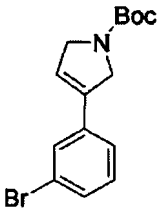
[1971]





[1972] 3-(3-溴苯基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯

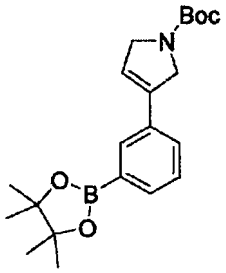
[1973]



[1974] 步骤1:1-溴-3-碘苯(956.0mg,3.4mmol)、3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(500.0mg,1.7mmol)、$Pd(dppf)Cl_2$(123.0mg,169.0μmol)及K_2CO_3(466.0mg,3.4mmol)于二恶烷(20.00mL)及H_2O(4.0mL)中的混合物在80℃下、在N_2保护下搅拌12小时。浓缩混合物,得到残余物,将其溶解于乙酸乙酯

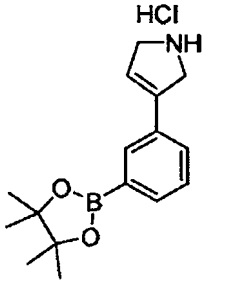
(50mL)及H_2O(30mL)中。分离水层且用乙酸乙酯(30mL×3)萃取。合并的有机层用盐水(25mL)洗涤,经无水Na_2SO_4干燥,过滤且浓缩,得到残余物,通过硅胶色谱纯化(乙酸乙酯/石油醚=0%至11%),得到呈黄色油状的产物3-(3-溴苯基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(450.0mg,82.2%产率)。

[1975] 3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯-1-甲酸叔丁酯

[1976] 

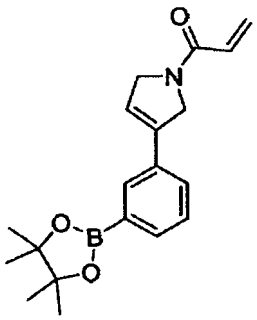
[1977] 步骤2:3-(3-溴苯基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(450.0mg,1.4mmol)、4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,3,2-二氧杂硼杂环戊烷(700.0mg,2.8mmol)、Pd(dppf)Cl_2(101.0mg,138.0μmol)及AcOK(202.0mg,2.1mmol)于二恶烷(20.00mL)中的混合物在100℃下、在N_2保护下搅拌12小时。浓缩混合物,得到残余物,将其溶解于乙酸乙酯(50mL)及H_2O(30mL)中。分离水层且用乙酸乙酯(30mL×3)萃取。合并的有机层用盐水(25mL)洗涤,经无水Na_2SO_4干燥,过滤且浓缩,得到残余物,通过硅胶色谱纯化(乙酸乙酯/石油醚=0%至12%),得到呈黄色油状的产物3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(450.0mg,87.8%产率)。

[1978] 3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯盐酸盐

[1979] 

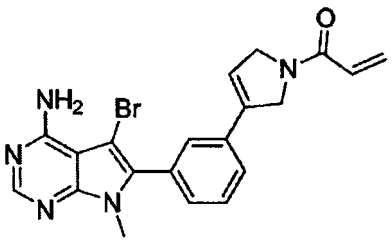
[1980] 步骤3:添加HCl/EtOAc(6.00mL,4M)中的3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(450.0,1.2mmol)。在25℃下搅拌混合物2小时。浓缩混合物,得到呈黄色油状的3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯盐酸盐(372.0mg,100%产率)。

[1981] 1-{3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯-1-基}丙-2-烯-1-酮

[1982] 

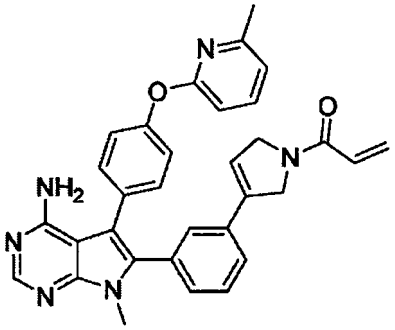
[1983] 步骤4:在0℃下,将DCM(3.00mL)中的丙-2-烯酰氯(140.0mg,1.6mmol)添加于3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯盐酸盐(372.0mg,1.2mmol)及DIEA(1.04mL,6.0mmol)于DCM(12.00mL)中的混合物中。在25℃下搅拌混合物4小时。混合物用DCM(20mL)稀释,用饱和$NaHCO_3$(20mL)、盐水(20mL)洗涤,经无水Na_2SO_4干燥,过滤且浓缩,得到残余物,通过硅胶色谱纯化(乙酸乙酯/石油醚=0%至45%),得到呈黄色油状的产物1-{3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯-1-基}丙-2-烯-1-酮(210.0mg,53.8%产率)。

[1984] 1-[3-(3-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)-2,5-二氢-1H-吡咯-1-基]丙-2-烯-1-酮

[1985] 

[1986] 步骤5:1-{3-[3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2,5-二氢-1H-吡咯-1-基}丙-2-烯-1-酮(210.0mg,645.0μmol)、5-溴-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(250.0mg,709.0μmol)、$Pd(PPh_3)_4$(74.4mg,64.5μmol)及K_3PO_4(271.0mg,1.28mmol)于DMF(16.00mL)及H_2O(4.00mL)中的混合物在50℃下、在N_2保护下搅拌12小时。混合物用乙酸乙酯(30mL)稀释,用H_2O(20mL×3)、盐水(15mL)洗涤,经无水Na_2SO_4干燥,过滤且浓缩,得到残余物,通过硅胶色谱纯化(甲醇/二氯甲烷=0%至14%),得到呈黄色油状的产物1-[3-(3-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)-2,5-二氢-1H-吡咯-1-基]丙-2-烯-1-酮(70.0mg,25.6%产率)。

[1987] 1-{3-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)苯基]-2,5-二氢-1H-吡咯-1-基}丙-2-烯-1-酮

[1988] 

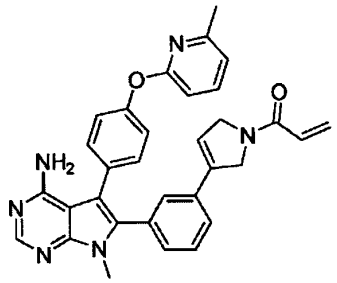
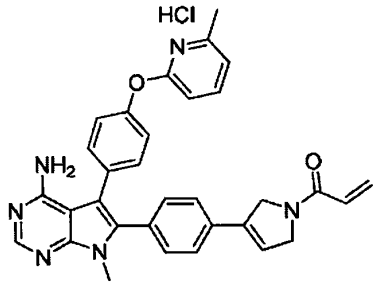
[1989] 1-[3-(3-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}苯基)-2,5-二氢-

1H-吡咯-1-基]丙-2-烯-1-酮(50.0mg,117.0μmol)、2-甲基-6-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]吡啶(54.4mg,175.0μmol)、$Pd_2(dba)_3$(10.7mg,117.0μmol)、XPhos(11.1mg,117.0μmol)、K_2CO_3(48.4mg,117.0μmol)于二恶烷(4.00mL)及H_2O(1.00mL)中的混合物在95℃下、在N_2保护下搅拌12小时。过滤混合物且浓缩滤液,得到残余物,通过制备型HPLC(HCl)纯化,得到呈白色固体状的产物1-{3-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)苯基]-2,5-二氢-1H-吡咯-1-基}丙-2-烯-1-酮(4.9mg,7.41%产率)。

[1990] 根据实例41的方法制备的其它化合物描绘于下表40中。

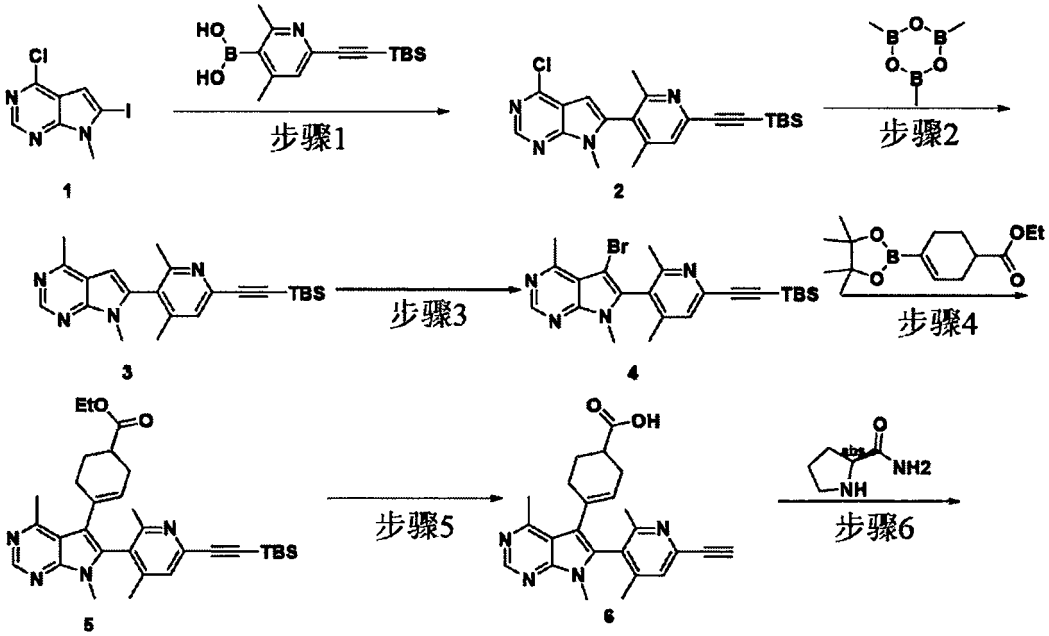
[1991] 表40.示例性化合物

[1992]

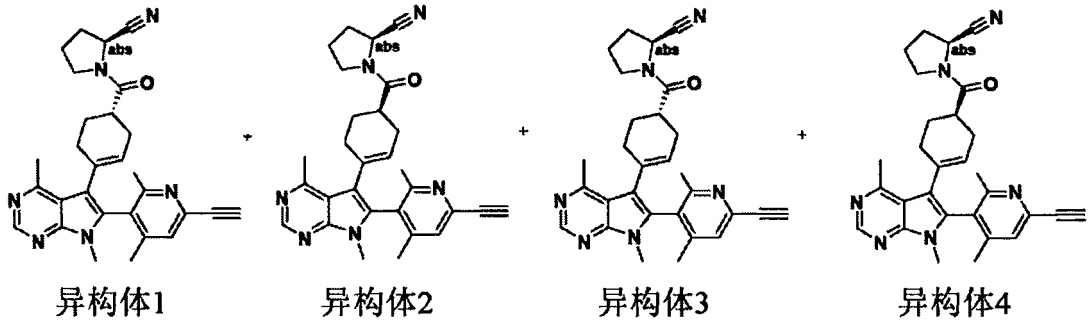
化合物	结构	质子 NMR	MS [M+1]
1-{3-[3-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]-2,5-二氢-1*H*-吡咯-1-基}丙-2-烯-1-酮		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.73-7.70 (m, 1H), 7.63-7.60 (d, *J* = 8.0 Hz, 1H), 7.49-7.45 (m, 2H), 7.35-7.28 (m, 3H), 7.32-7.28 (m, 3H), 7.14-7.10 (m, 2H), 7.02-7.00 (d, *J* = 7.6 Hz, 1H), 6.79-6.76 (m, 1H), 6.69-6.59 (m, 1H), 6.49 (s, 1H), 6.23-6.15 (m, 1H), 5.75-5.70 (m, 1H), 4.69 (s, 1H), 4.55-4.47 (d, *J* = 32.4 Hz, 2H), 4.32 (s, 1H), 3.75-3.73 (d, *J* = 6.8 Hz, 3H), 2.31-2.29 (d, *J* = 7.2 Hz, 3H).	529.3
1-{3-[4-(4-氨基-7-甲基-5-{4-[(6-甲基吡啶-2-基)氧基]苯基}-7*H*-吡咯并[2,3-*d*]嘧啶-6-基)苯基]-2,5-二氢-1*H*-吡咯-1-基}丙-2-烯-1-酮盐酸盐		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.13-8.07 (m, 1H), 7.6 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.32-7.27 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.81-6.64 (m, 1H), 6.49-6.36 (m, 2H), 5.87-5.82 (m, 1H), 4.79 (s, 1H), 4.67 (s, 2H), 4.49 (s, 1H), 3.83 (s, 3H), 2.61 (d, *J* = 3.2 Hz, 3H).	529.1

[1993] 实例42

[1994] 流程39

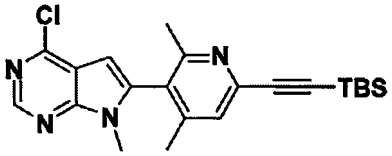


[1995]



[1996] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶

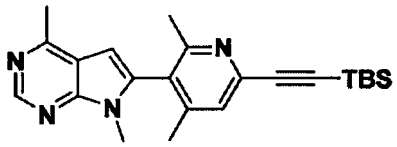
[1997]



[1998] 步骤1:向可再密封的反应瓶中装入4-氯-6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶(1.50g,5.11mmol)、{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}硼酸(1.62g,5.62mmol)、K_3PO_4(3.24g,15.3mmol)、PAd_2nBu(183mg,511μmol)、PAd_2nBu Pd-G2(341mg,511μmol)、DME/H_2O(20mL)及搅拌棒,随后抽真空且用氮气吹扫三次,且在70℃下搅拌混合物整夜。反应混合物用水(30mL)稀释,且水相用二氯甲烷(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/

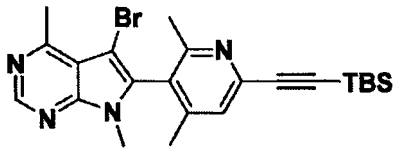
甲醇30:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的6-[2-(叔丁基二甲基硅烷基)乙炔基]-3-{4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2,4-二甲基吡啶(1.50g,65%)。

[1999] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[2000] 

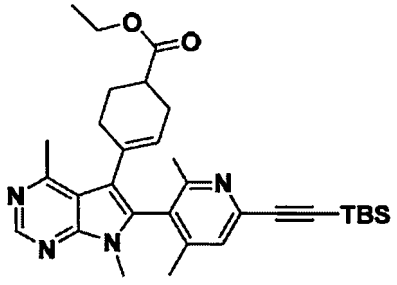
[2001] 步骤2:向可再密封的反应瓶中装入6-[2-(叔丁基二甲基硅烷基)乙炔基]-3-{4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2,4-二甲基吡啶(3.50g,8.51mmol)、四氢呋喃(40mL)、K_3PO_4(5.40g,25.5mmol)、Pd(dppf)Cl_2(622mg,851μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加三甲基-1,3,5,2,4,6-三氧杂三硼杂环己烷(50%)(6.4g,25.5mmol),且在70℃下搅拌混合物2小时。反应混合物用水(50mL)稀释,且水相用DCM(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇80:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的6-[2-(叔丁基二甲基硅烷基)乙炔基]-3-{4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2,4-二甲基吡啶(2.80g,84%)。

[2002] 5-溴-6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[2003] 

[2004] 步骤3:向圆底烧瓶中装入6-[2-(叔丁基二甲基硅烷基)乙炔基]-3-{4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-2,4-二甲基吡啶(2.80g,7.16mmol)、二甲基甲酰胺(30mL)及搅拌棒。然后添加NBS(1.39g,7.87mmol),且在25℃下搅拌溶液1小时。反应混合物用Na_2SO_3(水溶液)(30mL)淬灭,且反应混合物经由硅藻土垫过滤,用水洗涤垫,且真空干燥滤饼,产生呈黄色无定形固体状的3-{5-溴-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶(3.02g,90%)。

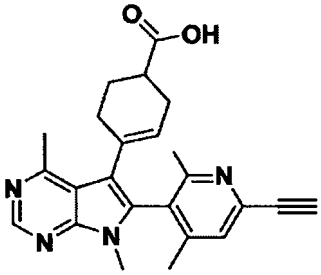
[2005] 4-(6-(6-((叔丁基二甲基硅烷基)乙炔基)-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-甲酸乙酯

[2006] 

[2007] 步骤4:向可再密封的反应瓶中装入3-{5-溴-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶(3.00g,6.38mmol)、DME/H_2O(30mL)、4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)环己-3-烯-1-甲酸乙酯

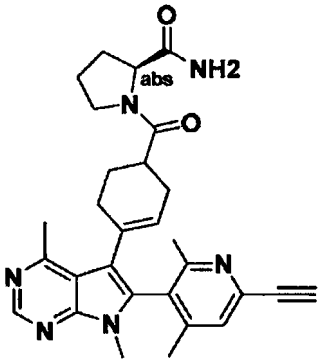
(1.96g,7.01mmol)、K_3PO_4(4.04g,19.1mmol)、Pd(dppf)Cl_2(466mg,638μmol)及搅拌棒,随后抽真空且用氮气吹扫三次,且在70℃下搅拌混合物1小时。反应混合物用水(30mL)稀释,且水相用二氯甲烷(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇40:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的4-(6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-甲酸乙酯(2.50g,72%)。

[2008] 4-(6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-甲酸

[2009] 

[2010] 步骤5:向圆底烧瓶中装入4-(6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-2,4-二甲基吡啶-3-基}-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-甲酸乙酯(2.48g,4.56mmol)、NaOH(543mg,13.6mmol)及搅拌棒。添加MeOH/H_2O(20mL),且在60℃下搅拌溶液1小时。将反应混合物pH调节至5~6,真空浓缩,产生呈黑色无定形固体状的4-[6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-甲酸(2.2g,粗物质)。

[2011] (2S)-1-(4-(6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲酰胺

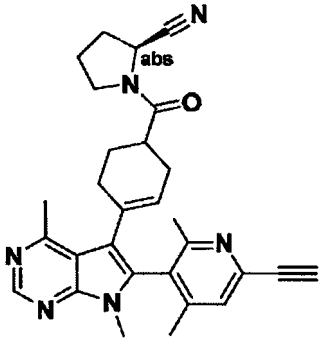
[2012] 

[2013] 步骤6:向圆底烧瓶中装入4-[6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-甲酸(1.7g,4.24mmol)、二甲基甲酰胺(20mL)、T3P(5.38g,8.48mmol)、TEA(856mg,8.48mmol)及搅拌棒。添加(2S)-吡咯烷-2-甲酰胺(967mg,8.48mmol),且在25℃下搅拌溶液1小时。反应混合物用水(30mL)稀释,且水相用二氯甲烷(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(乙腈/水/0.1%甲酸)。冻干,产生呈黑色无定形固体状的(2S)-1-{4-[6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-羰基}吡咯烷-2-甲酰胺(1.5g,71%)。

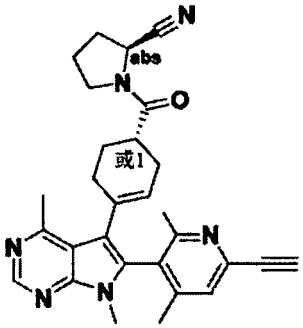
[2014] (2S)-1-(4-(6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-

d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈

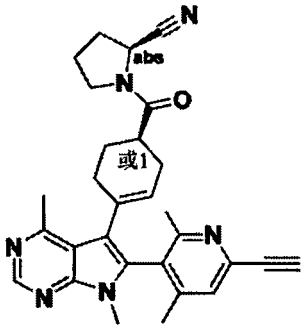
[2015]



[2016] 步骤7:向可再密封的反应瓶中装入(2S)-1-{4-[6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-羰基}吡咯烷-2-甲腈(320mg,668μmol)、四氢呋喃(5mL)及搅拌棒,随后抽真空且用氮气吹扫三次,添加伯格斯试剂(Burgess reagent)(316mg,1.34mmol),且在25℃下搅拌混合物2小时。反应混合物用水(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型HPLC纯化(柱:XBridge Prep OBD C18柱,30×150mm 5um;移动相A:水(10MMOL/LNH_4HCO_3+0.1%$NH_3 \cdot H_2O$),移动相B:ACN;流量:60mL/min;梯度:20B至45B,历时8min;220nm;RT1:7.23;RT2:;注射体积:ml;操作次数:;)。冻干产生呈灰白色无定形固体状的(2S)-1-{4-[6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基]环己-3-烯-1-羰基}吡咯烷-2-甲腈(160mg,50%)。

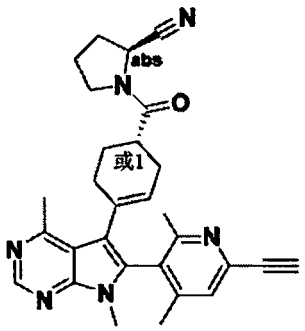


异构体1

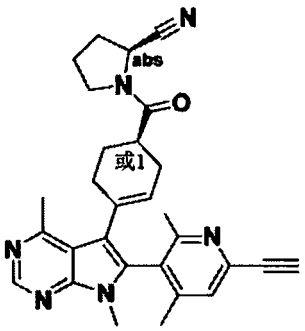


异构体2

[2017]



异构体3



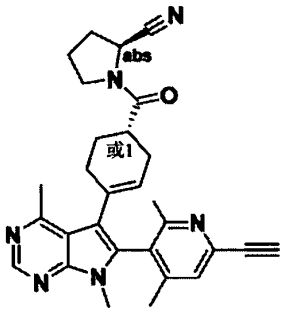
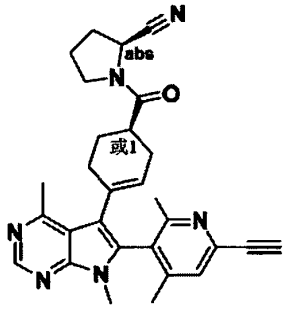
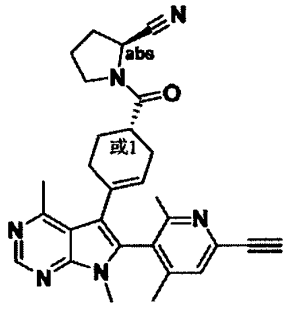
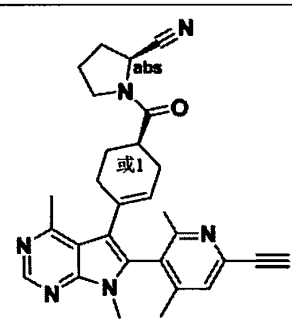
异构体4

[2018] 步骤8:将所得物质(160mg)送交手性分离(柱:CHIRALPAK IF,2*25cm,5um;移动相

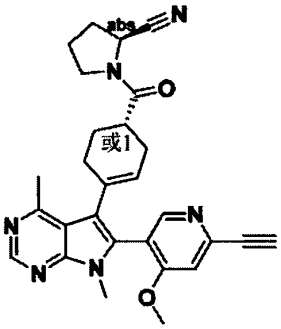
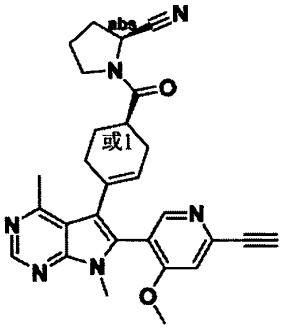
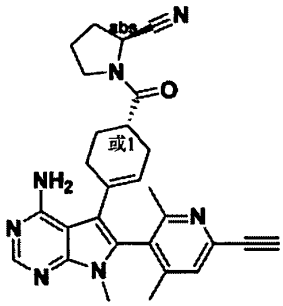
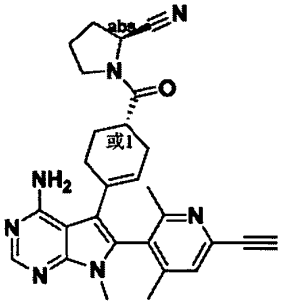
A:Hex(0.5%2M NH3-MeOH)--HPLC,移动相B:EtOH:DCM=1:1--HPLC;流量:20mL/min;梯度:35B至35B,历时11分钟;220/254nm;RT1:6.855;RT2:8.514;注射体积:0.7ml;操作次数:6;)。冻干产生峰1(76mg)、峰2(67mg)。然后再次进行手性分离操作:峰1(柱:CHIRAL ART纤维素-SB S-5um,2*25cm,5um;移动相A:Hex(0.5%2M NH3-MeOH)--HPLC,移动相B:EtOH:DCM=1:1--HPLC;流量:20mL/min;梯度:20B至20B,历时17分钟;220/254nm;RT1:13.481;RT2:15.128;注射体积:0.65ml;操作次数:5);产生呈灰白色无定形固体状的异构体2(27.2mg)及异构体4(25mg)。峰2(柱:CHIRALART纤维素-SB,2*25cm,5um;移动相A:Hex(0.5%2MNH3-MeOH)--HPLC,移动相B:EtOH:DCM=1:1--HPLC;流量:20mL/min;梯度:20B至20B,历时18分钟;220/254nm;RT1:13.832;RT2:15.921;注射体积:0.7ml;操作次数:6);产生呈灰白色无定形固体状的异构体1(25.7mg)及异构体3(21.4mg)。

[2019] 表41.示例性化合物

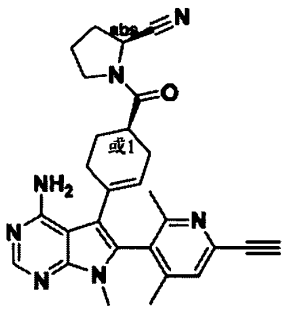
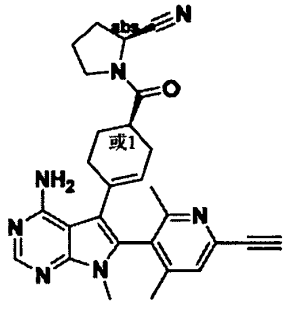
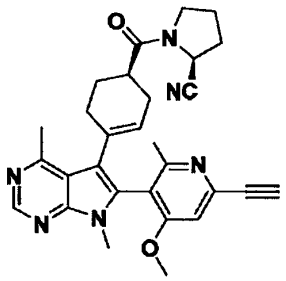
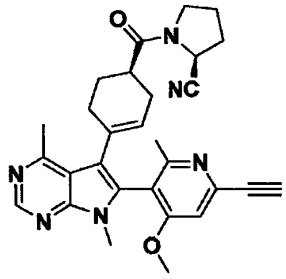
[2020]

化合物	结构	质子 NMR	MS [M+1]
(S)-1-((S)-4-(6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 异构体1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.50 (s, 1H), 5.68 (s, 1H), 4.70 (dd, J = 7.7, 3.5 Hz, 1H), 4.39 (s, 1H), 3.67 (ddd, J = 9.6, 7.0, 4.5 Hz, 1H), 3.54 - 3.44 (m, 1H), 3.42 (s, 3H), 2.68 (d, J = 3.5 Hz, 3H), 2.60 (d, J = 9.3 Hz, 1H), 2.20 (d, J = 2.8 Hz, 5H), 2.18 - 2.07 (m, 3H), 2.06 - 1.94 (m, 6H), 1.76 (d, J = 13.1 Hz, 1H), 1.53 - 1.37 (m, 1H).	479.25
(S)-1-((R)-4-(6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 异构体2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.50 (s, 1H), 5.67 (s, 1H), 4.71 (dd, J = 7.6, 3.7 Hz, 1H), 4.39 (s, 1H), 3.63 (ddd, J = 11.3, 7.0, 4.4 Hz, 1H), 3.56 - 3.46 (m, 1H), 3.42 (s, 3H), 2.69 (s, 3H), 2.59 (s, 1H), 2.19 (s, 6H), 2.18 - 2.06 (m, 3H), 2.04 (s, 3H), 2.00 (dd, J = 7.4, 3.4 Hz, 2H), 1.80 (d, J = 13.0 Hz, 1H), 1.57 - 1.45 (m, 1H).	479.25
(S)-1-((S)-4-(6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 异构体3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.49 (s, 1H), 5.64 (s, 1H), 4.71 (dd, J = 7.6, 3.7 Hz, 1H), 4.39 (s, 1H), 3.64 (ddd, J = 11.4, 7.2, 4.6 Hz, 1H), 3.51 (q, J = 8.0 Hz, 1H), 3.41 (s, 3H), 2.68 (s, 3H), 2.60 (s, 1H), 2.19 (d, J = 2.2 Hz, 5H), 2.12 (tq, J = 13.0, 5.1, 3.3 Hz, 4H), 2.04 (s, 3H), 1.99 (dd, J = 10.0, 6.1 Hz, 2H), 1.81 (d, J = 13.2 Hz, 1H), 1.50 (dd, J = 12.0, 5.2 Hz, 1H).	479.30
(S)-1-((R)-4-(6-(6-乙炔基-2,4-二甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 异构体4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.50 (s, 1H), 5.68 (s, 1H), 4.70 (dd, J = 7.7, 3.6 Hz, 1H), 4.40 (s, 1H), 3.71 - 3.61 (m, 1H), 3.55 - 3.44 (m, 1H), 3.42 (s, 3H), 2.70 (d, J = 3.5 Hz, 3H), 2.60 (d, J = 8.7 Hz, 1H), 2.19 (s, 5H), 2.17 - 2.07 (m, 4H), 2.04 (s, 3H), 2.01 (dd, J = 9.6, 5.3 Hz, 2H), 1.77 (d, J = 12.9 Hz, 1H), 1.48 (td, J = 11.8, 5.5 Hz, 1H).	479.25

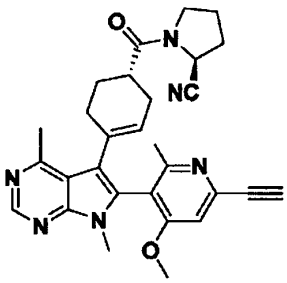
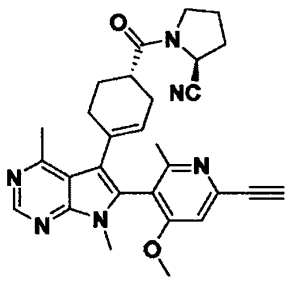
[2021]

化合物	结构	质子 NMR	MS [M+1]
(S)-1-((S)-4-(6-(6-乙炔基-4-甲氧基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.33 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 1.4 Hz, 1H), 5.64 (d, J = 23.1 Hz, 1H), 4.73 (dd, J = 7.6, 3.7 Hz, 1H), 4.47 (s, 1H), 3.91 (d, J = 1.7 Hz, 3H), 3.51 (s, 4H), 2.66 (d, J = 2.8 Hz, 3H), 2.28 - 2.11 (m, 4H), 2.08 (s, 2H), 2.02 (s, 2H), 1.83 (s, 1H), 1.66 - 1.45 (m, 2H), 1.45 - 1.34 (m, 1H), 1.24 (s, 1H).	481.4
S)-1-((R)-4-(6-(6-乙炔基-4-甲氧基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 3.4 Hz, 1H), 5.66 (d, J = 14.2 Hz, 1H), 4.72 (dd, J = 7.8, 3.5 Hz, 1H), 4.48 (d, J = 1.3 Hz, 1H), 3.91 (d, J = 2.0 Hz, 3H), 3.68 (s, 1H), 3.52 (s, 4H), 2.66 (s, 4H), 2.20 (s, 3H), 2.14 (d, J = 7.8 Hz, 2H), 2.08 (s, 1H), 2.02 (d, J = 8.5 Hz, 3H), 1.80 (s, 1H), 1.54 (d, J = 8.2 Hz, 1H), 1.45 - 1.39 (m, 1H), 1.24 (s, 1H), 1.16 (d, J = 7.2 Hz, 1H).	481.25
(S)-1-((S)-4-(4-氨基-6-(6-乙炔基-2,4-二甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈 异构体1		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.47 (s, 1H), 6.55 (s, 2H), 5.65 (q, J = 2.8, 2.2 Hz, 1H), 4.70 (dd, J = 7.4, 3.4 Hz, 1H), 4.38 (s, 1H), 3.69 (ddd, J = 10.9, 7.4, 3.8 Hz, 1H), 3.47 (td, J = 8.9, 6.7 Hz, 1H), 3.31 (s, 3H), 2.79 (t, J = 6.2 Hz, 1H), 2.24 (s, 2H), 2.19 (s, 3H), 2.13 (ddd, J = 9.8, 6.7, 3.5 Hz, 2H), 2.03 (s, 5H), 1.90 (s, 2H), 1.61 (s, 2H).	480.25
(S)-1-((S)-4-(4-氨基-6-(6-乙炔基-2,4-二甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈 异构体2		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.47 (s, 1H), 6.58 (s, 2H), 5.66 (s, 1H), 4.70 (dd, J = 7.4, 3.6 Hz, 1H), 4.38 (s, 1H), 3.74 - 3.65 (m, 1H), 3.47 (q, J = 8.6 Hz, 1H), 3.31 (s, 3H), 2.88 (s, 1H), 2.25 (s, 2H), 2.21 - 2.09 (m, 5H), 2.04 (s, 5H), 1.88 (s, 2H), 1.60 (d, J = 9.4 Hz, 2H).	480.25

[2022]

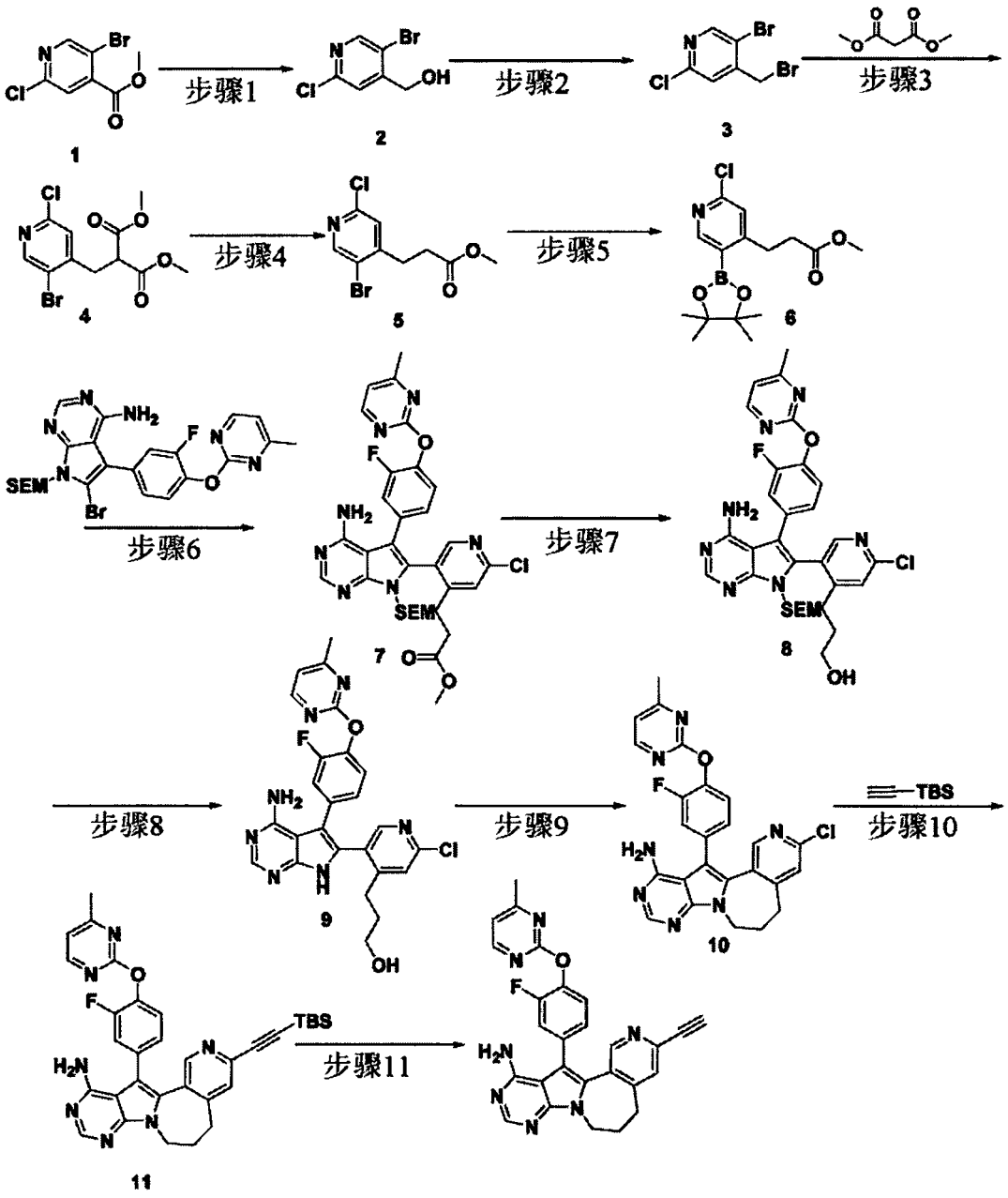
化合物	结构	质子 NMR	MS [M+1]
(S)-1-((R)-4-(4-氨基-6-(6-乙炔基-2,4-二甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 异构体3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.48 (s, 1H), 6.72 (s, 2H), 5.66 (s, 1H), 4.71 (dd, J = 7.9, 3.7 Hz, 1H), 4.38 (s, 1H), 3.60 (t, J = 6.1 Hz, 1H), 3.53 (q, J = 8.1 Hz, 1H), 3.32 (s, 3H), 2.84 - 2.77 (m, 1H), 2.25 (s, 2H), 2.18 (s, 4H), 2.05 (s, 3H), 2.04 - 1.96 (m, 2H), 1.89 (s, 2H), 1.63 (d, J = 6.3 Hz, 2H), 1.16 (t, J = 7.3 Hz, 1H).	480.25
(S)-1-((R)-4-(4-氨基-6-(6-乙炔基-2,4-二甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 异构体4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.47 (s, 1H), 6.72 (s, 2H), 5.65 (s, 1H), 4.71 (dd, J = 7.9, 3.7 Hz, 1H), 4.39 (s, 1H), 3.61 (dd, J = 10.4, 4.6 Hz, 1H), 3.53 (q, J = 8.5, 8.0 Hz, 1H), 3.32 (s, 3H), 2.80 (t, J = 6.1 Hz, 1H), 2.24 (s, 1H), 2.20 (s, 5H), 2.05 - 1.95 (m, 5H), 1.91 (s, 2H), 1.64 (s, 2H), 1.16 (t, J = 7.3 Hz, 1H).	480.25
(S)-1-((R)-4-(6-(6-乙炔基-4-甲氧基-2-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 滞转异构体 1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 1.4 Hz, 1H), 7.28 (s, 1H), 5.60 (s, 1H), 4.70 (t, J = 7.7, 3.5 Hz, 1H), 4.41 (d, J = 1.1 Hz, 1H), 3.81 (s, 3H), 3.70 - 3.57 (m, 1H), 3.51 (t, J = 8.5 Hz, 1H), 3.41 (s, 3H), 2.68 - 2.56 (m, 4H), 2.27 - 2.08 (m, 6H), 2.04 (d, J = 15.4 Hz, 6H), 1.79 (d, J = 13.1 Hz, 1H).	495.25
(S)-1-((R)-4-(6-(6-乙炔基-4-甲氧基-2-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 滞转异构体 2	^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (s, 1H), 7.28 (s, 1H), 5.58 (s, 1H), 4.71 (dd, J = 7.6, 3.7 Hz, 1H), 4.41 (s, 1H), 3.82 (d, J = 2.3 Hz, 3H), 3.70 - 3.59 (m, 1H), 3.51 (q, J = 8.2 Hz, 1H), 3.42 (s, 3H), 2.66 (d, J = 3.3 Hz, 3H), 2.56 (s, 1H), 2.17 (s, 5H), 2.15 - 2.05 (m, 4H), 2.02 (t, J = 7.0 Hz, 2H), 1.81 (d, J = 13.1 Hz, 1H), 1.56 (d, J = 6.6 Hz, 1H).	495.30

[2023]

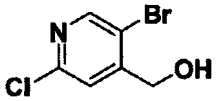
化合物	结构	质子 NMR	MS [M+1]
(S)-1-((S)-4-(6-(6-乙炔基-4-甲氧基-2-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 滞转异构体 1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.28 (s, 1H), 5.60 (s, 1H), 4.71 (dd, J = 7.7, 3.5 Hz, 1H), 4.42 (s, 1H), 3.82 (s, 3H), 3.67 (ddd, J = 9.5, 7.2, 4.4 Hz, 1H), 3.49 (dd, J = 9.4, 7.3 Hz, 1H), 3.42 (s, 3H), 2.66 (d, J = 2.5 Hz, 3H), 2.62 - 2.56 (m, 1H), 2.17 (d, J = 2.2 Hz, 4H), 2.16 - 1.95 (m, 6H), 1.78 (dd, J = 13.1, 3.3 Hz, 1H), 1.61 - 1.43 (m, 2H).	495.25
(S)-1-((S)-4-(6-(6-乙炔基-4-甲氧基-2-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶-5-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈	 滞转异构体 2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 7.28 (s, 1H), 5.60 (d, J = 25.9 Hz, 1H), 4.71 (d, J = 6.4 Hz, 1H), 4.42 (s, 1H), 3.82 (s, 3H), 3.66 (s, 1H), 3.59 - 3.50 (m, 1H), 2.91 (s, 1H), 2.65 (s, 3H), 2.17 (s, 5H), 2.10 (d, J = 14.7 Hz, 2H), 2.01 (s, 2H), 1.79 (d, J = 24.2 Hz, 1H), 1.45 (s, 1H), 1.24 (s, 4H), 1.15 (d, J = 9.2 Hz, 1H).	495.30

[2024] 实例43

[2025] 流程40

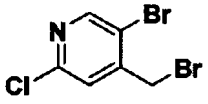
[2026] 

[2027] (5-溴-2-氯吡啶-4-基)甲醇

[2028] 

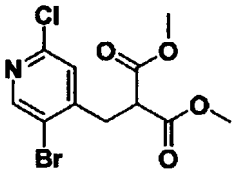
[2029] 步骤1:将5-溴-2-氯吡啶-4-甲酸甲酯(75.0g,299mmol)于THF(1.5L)中的溶液冷却至-20℃。历经1.5小时时间段逐滴添加$LiBH_4$(179mL,358mmol,2M于THF中),同时维持温度低于-15℃。使溶液升温至室温且在25℃下搅拌2小时,然后通过逐滴添加饱和NH_4Cl(200mL)小心地淬灭,且用EtOAc(1.2L)萃取水相三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(450g柱;用石油醚:乙酸乙酯10:1洗脱)。真空浓缩,产生呈灰白色无定形固体状的(5-溴-2-氯吡啶-4-基)甲醇(40g,60.1%)。

[2030] 5-溴-4-(溴甲基)-2-氯吡啶

[2031] 

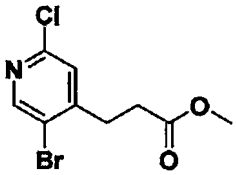
[2032] 步骤2:在0℃下,向(5-溴-2-氯吡啶-4-基)甲醇(54.0g,242)及CBr_4(87.2g,266mmol)于DCM(1.5L)中的混合物中逐滴添加含PPh3(69.6g,266mmol)的DCM(300mL),在0℃下搅拌1小时。用盐水(500mL)淬灭反应物。分离所分溶的层。用DCM(1L×3)萃取水相。合并的有机层用盐水(1L)洗涤,经无水Na_2SO_4干燥,过滤且浓缩,得到残余物。残余物通过急骤硅胶色谱来纯化(石油醚:乙酸乙酯=30:1),得到呈白色固体状的产物5-溴-4-(溴甲基)-2-氯吡啶(51g,73.9%)。

[2033] 2-[(5-溴-2-氯吡啶-4-基)甲基]丙二酸1,3-二甲酯

[2034] 

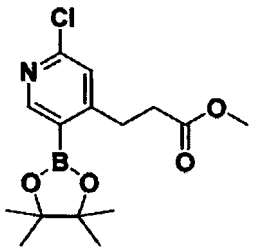
[2035] 步骤3:在-10℃下,向丙二酸1,3-二甲酯(62.0g,470mmol)于THF(900mL)中的混合物中添加NaH(18.6g,470mmol),在-10℃下搅拌30分钟,然后添加含5-溴-4-(溴甲基)-2-氯吡啶(45.0g,157mmol)的300mL。将THF逐滴添加至上述溶液中且搅拌2小时。用饱和NH4Cl(600mL)淬灭混合物。用EtOAc(1L)萃取水相三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(500g柱;用石油醚:乙酸乙酯=15:1洗脱)。真空浓缩,产生呈灰白色无定形固体状的2-[(5-溴-2-氯吡啶-4-基)甲基]丙二酸1,3-二甲酯(40g,75.7%)。

[2036] 3-(5-溴-2-氯吡啶-4-基)丙酸甲酯

[2037] 

[2038] 步骤4:向圆底烧瓶中装入2-[(5-溴-2-氯吡啶-4-基)甲基]丙二酸1,3-二甲酯(39.5g,117mmol)、NaCl(20.3g,351mmol)、H20(6.31g,351mmol)及搅拌棒。添加DMSO(800mL),且在160℃下搅拌溶液1小时。反应混合物用EtOAc(1.5L)稀释,且水相用盐水(600mL)洗涤四次。合并的有机层经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(300g柱;用石油醚/乙酸乙酯15:1洗脱)。真空浓缩,产生呈白色无定形固体状的3-(5-溴-2-氯吡啶-4-基)丙酸甲酯(22.0g,67%)。

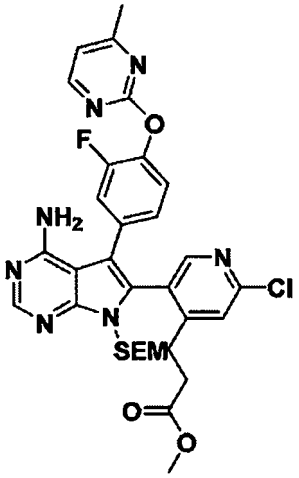
[2039] 3-(2-氯-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-4-基)丙酸甲酯

[2040] 

[2041] 步骤5:向可再密封的反应瓶中装入3-(5-溴-2-氯吡啶-4-基)丙酸甲酯(10g,

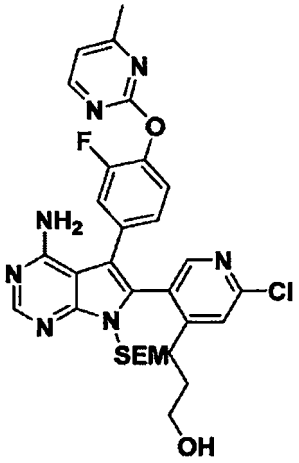
35.9mmol)、4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,3,2-二氧杂硼杂环戊烷(11.8g,46.6mmol)、Pd(dppf)Cl_2(2.62,3.59mmol)、KOAc(10.4g,107mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷(200mL),且在70℃下搅拌混合物12小时。通过硅藻土垫过滤收集催化剂及盐且用EtOAc(100mL)洗涤三次。合并的有机层经Na_2SO_4干燥,过滤且在减压下蒸发。所得粗物质通过硅胶色谱纯化(200g柱;用石油醚/乙酸乙酯15:1洗脱)。真空浓缩,产生呈白色无定形固体状的3-[2-氯-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-4-基]丙酸甲酯(6.5g,56.0%)。

[2042] 3-(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基)丙酸甲酯

[2043] 

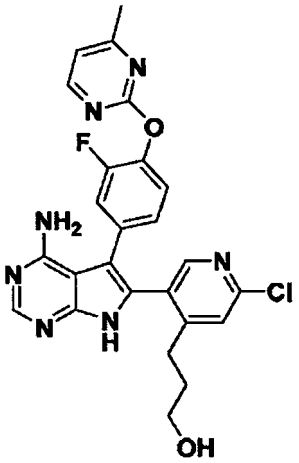
[2044] 步骤6:向可再密封的反应瓶中装入6-溴-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(14.5g,26.5mmol)、3-[2-氯-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-4-基]丙酸甲酯(12.9g,39.7mmol)、Pd(DTBPF)Cl2(1.72g,2.65mmol)、CsF(12.0g,79.5mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加THF/H2O(300mL),且在70℃下搅拌混合物12小时。反应混合物用水(100mL)稀释,且水相用二氯甲烷(500mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(200g柱;用二氯甲烷/甲醇20:1洗脱)。真空浓缩,产生呈棕色无定形固体状的3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙酸甲酯(7.00g,40%)。

[2045] 3-(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基)丙-1-醇

[2046] 

[2047] 步骤7:向圆底烧瓶中装入3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙酸甲酯(7.00g,10.5mmol)、DCM(120mL)及搅拌棒。在0℃下添加DIBAL(8.39mL,12.6mmol),且在0℃下搅拌溶液3小时。反应混合物用MeOH(10mL)及水(60mL)稀释,且水相用二氯甲烷(100mL)萃取三次。将合并的有机层过滤且用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过C18flash来纯化(乙腈/水/0.1%甲酸)。冻干产生呈黄色无定形固体状的3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(3.00g,45%)。

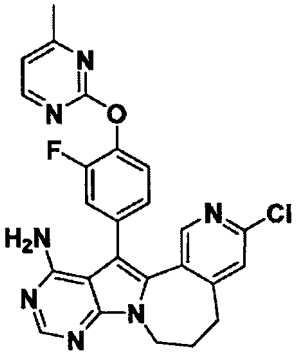
[2048] 3-(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基)丙-1-醇

[2049] 

[2050] 步骤8:向圆底烧瓶中装入3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(2.60g,4.08mmol)、CH3SO3H/THF(40mL)及搅拌棒。在70℃下搅拌溶液1小时。反应混合物用水(100mL)稀释,且水相用Na2CO3将pH值调节至7,用DCM(150mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用二氯甲烷/甲醇12:1洗脱)。真空浓缩产生呈灰白色无定形固体状的3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(800mg,39%)。

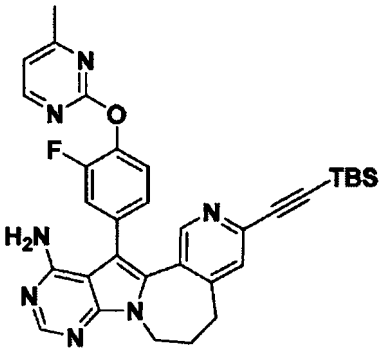
[2051] 3-氯-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-

c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2052] 

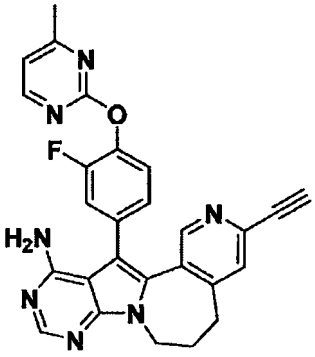
[2053] 步骤9:向可再密封的反应瓶中装入3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(680mg,1.34mmol)、DIAD(406mg,2.01mmol)、四氢呋喃(8mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加含PPh3(526mg,2.01mmol)的2mL THF,且在25℃下搅拌混合物1小时。反应混合物用水(5mL)稀释,且水相用DCM(25mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型TLC(二氯甲烷/甲醇15:1)来纯化。真空浓缩,产生呈黄色无定形固体状的3-氯-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(450mg,69%)。

[2054] 3-((叔丁基二甲基硅烷基)乙炔基)-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2055] 

[2056] 步骤10:向可再密封的反应瓶中装入3-氯-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(430mg,881μmol)、叔丁基(乙炔基)二甲基硅烷(246mg,1.76mmol)、Pd(dppf)Cl2(128mg,176μmol)、CuI(66.8mg,352μmol)、TEA(266mg,2.64mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二甲基甲酰胺(1mL),且在50℃下搅拌混合物2小时。反应混合物用水(5mL)稀释,且水相用DCM(25mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型TLC(二氯甲烷/甲醇15:1)来纯化。真空浓缩,产生呈灰白色无定形固体状的3-((叔丁基二甲基硅烷基)乙炔基)-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(350mg,67%)。

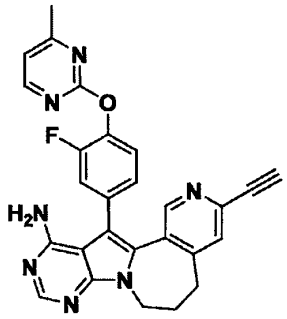
[2057] 3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2058] 

[2059] 步骤11:向圆底烧瓶中装入3-((叔丁基二甲基硅烷基)乙炔基)-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(340mg,574μmol)、四氢呋喃(2mL)及搅拌棒。添加TBAF(179mg,688μmol),且在室温下搅拌溶液1小时。反应混合物通过硅胶色谱纯化(20g柱;用二氯甲烷/甲醇10:1洗脱)。真空浓缩且粗产物用DMF(3mL)溶解,过滤且滤饼用ACN(10mL)及DCM(10mL)洗涤三次,在减压下干燥。冻干产生呈黄色无定形固体状的3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(173.1mg,362μmol,63.1%)。

[2060] 表42.示例性化合物

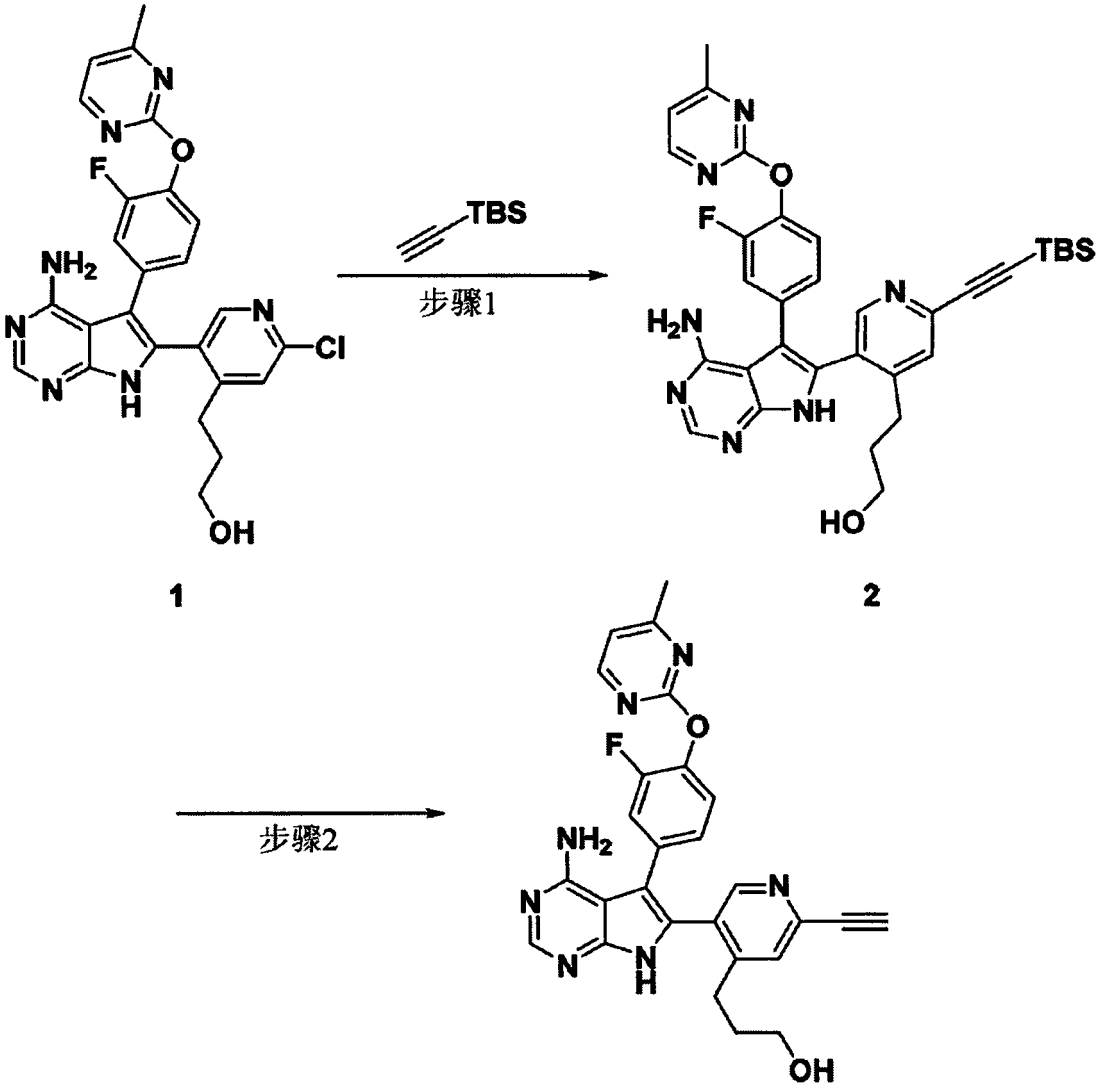
[2061]

化合物	结构	质子 NMR	MS [M+1]
3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5',4':4,5]吡咯并[1,2-a]氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 8.04 (s, 1H), 7.67 (s, 1H), 7.50 - 7.34 (m, 2H), 7.24 - 7.20 (m, 2H), 6.36 - 5.89 (m, 1H), 5.76 (s, 1H), 4.40 (s, 1H), 4.15 (s, 2H), 2.79 (t, J = 7.0 Hz, 2H), 2.44 (s, 3H), 2.25 (t, J = 7.1 Hz, 2H).	478.10

[2062] 实例44

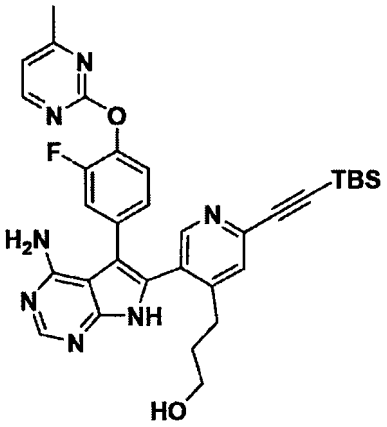
[2063] 流程41

[2064]



[2065] 3-(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-((叔丁基二甲基硅烷基)乙炔基)吡啶-4-基)丙-1-醇

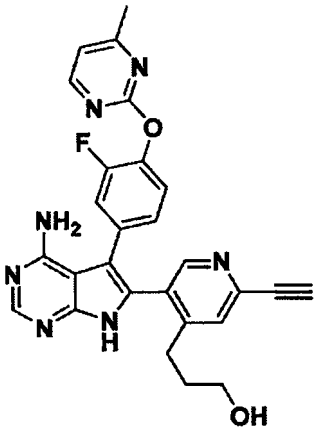
[2066]



[2067] 步骤1:向可再密封的反应瓶中装入3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]丙-1-醇(90.0mg,177μmol)、Pd(dppf)Cl2(25.9mg,35.4μmol)、CuI(13.4mg,70.8μmol)、TEA(53.6mg,531μmol)、叔丁基(乙炔基)二甲基硅烷(49.6mg,354μmol)、搅拌棒,随后抽真空且用氮气吹扫三次。添加二甲基甲酰胺(5mL),且在50℃下搅拌混合物2小时。反应混合物用水(20mL)稀释,且水相用

二氯甲烷(25mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型TLC(二氯甲烷/甲醇15:1)来纯化。真空浓缩,产生呈黄色无定形固体状的3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-[2-(叔丁基二甲基硅烷基)乙炔基]吡啶-4-基]丙-1-醇(80.0mg,74%)。

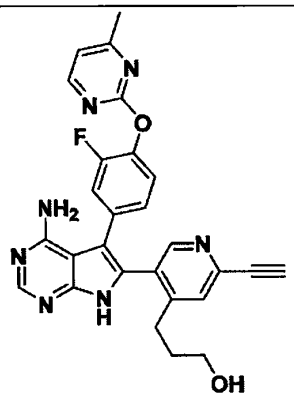
[2068] 3-(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)丙-1-醇

[2069] 

[2070] 步骤2:向圆底烧瓶中装入3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-[2-(叔丁基二甲基硅烷基)乙炔基]吡啶-4-基]丙-1-醇(70.0mg,114μmol)、四氢呋喃(5mL)及搅拌棒。添加TBAF(35.3mg,136μmol),且在室温下搅拌溶液1小时。反应物质通过硅胶色谱纯化(10g柱;用二氯甲烷/甲醇10:1洗脱)。真空浓缩且粗产物用水洗涤5次,浓缩有机相且所得粗物质通过制备型HPLC纯化(柱:XBridge Prep OBD C18柱,30×150mm 5um;移动相A:水(10MMOL/L NH_4HCO_3+0.1%$NH_3 \cdot H_2O$),移动相B:ACN;流量:60mL/min;梯度:15B至45B,历时8分钟;220nm;RT1:7.23)。冻干产生呈白色无定形固体状的3-[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基]丙-1-醇(11.2mg,19.8%)。

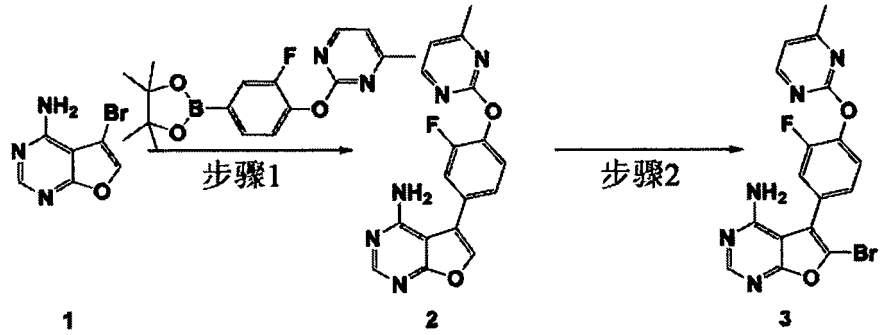
[2071] 表43.示例性化合物

[2072]

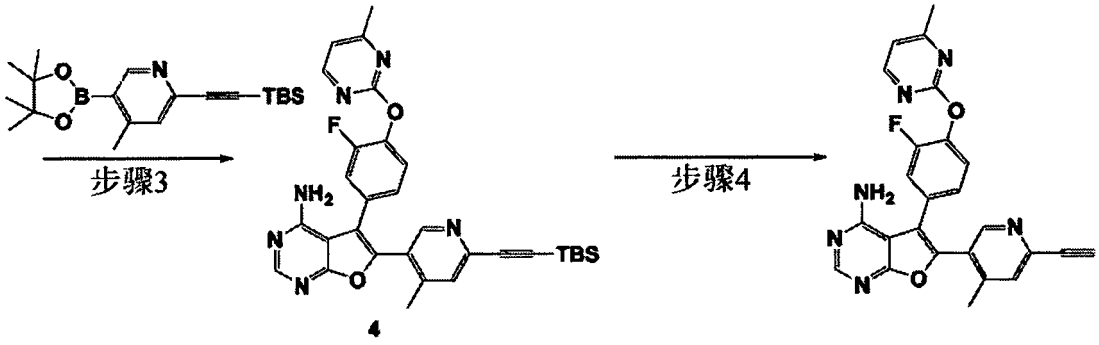
化合物	结构	质子 NMR	MS [M+1]
3-(5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)丙-1-醇		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.37 (s, 1H), 8.19 (s, 1H), 7.51 (s, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.06 (dd, J = 8.0, 2.0 Hz, 1H), 6.10 - 6.00(m, 1H), 4.44 (s, 1H), 4.39 (s, 1H), 3.30 - 3.10 (m, 4H), 2.42 (s, 3H), 1.53 - 1.47 (m, 2H).	496.25

[2073] 实例45

[2074] 流程42

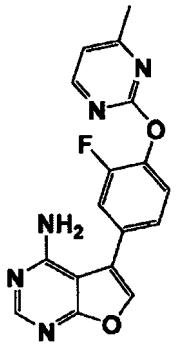


[2075]



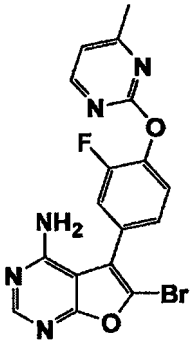
[2076] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)呋喃并[2,3-d]嘧啶-4-胺

[2077]



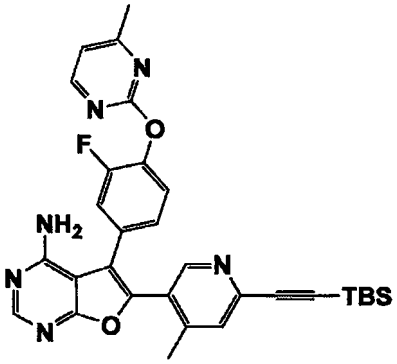
[2078] 步骤1:向可再密封的反应瓶中装入5-溴呋喃并[2,3-d]嘧啶-4-胺(800mg,3.73mmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(1.84g,5.59mmol)、Pd(dppf)Cl_2(2.72g,3.73mmol)、K_3PO_4(790mg,3.73mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(15mL),且在90℃下搅拌混合物2小时。反应混合物用水(100mL)稀释,且水相用DCM(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(100g柱;用庚烷/乙酸乙酯洗脱;比率=1:1)。真空浓缩,产生呈灰白色无定形固体状的5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺(800mg,64%)。

[2079] 6-6-溴-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)呋喃并[2,3-d]嘧啶-4-胺

[2080] 

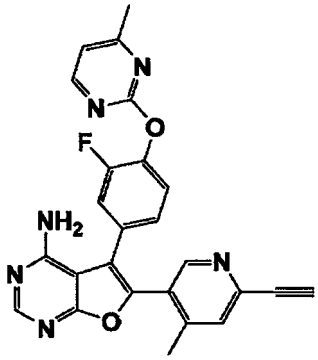
[2081] 步骤2:向圆底烧瓶中装入5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺(800mg,2.37mmol)、DCM(15mL)及搅拌棒。在0℃下添加Br_2(379mg,2.37mmol),且在0℃下搅拌溶液1小时。然后通过饱和硫代硫酸钠水溶液淬灭反应。反应混合物用水(100mL)稀释,且水相用DCM(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型HPLC(乙腈/水/0.1%甲酸)纯化。冻干产生呈灰白色无定形固体状的6-溴-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺(700mg,71%)。

[2082] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)呋喃并[2,3-d]嘧啶-4-胺

[2083] 

[2084] 步骤3:向可再密封的反应瓶中装入6-溴-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺(680mg,1.63mmol)、2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(872mg,2.44mmol)、Pd(dppf)Cl_2(238mg,0.326mmol)、K_3PO_4(1.03g,4.89mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H2O(20mL),且在90℃下搅拌混合物1小时。所得粗物质通过硅胶色谱纯化(50g柱;用二氯甲烷/甲醇洗脱;比率=30:1)。真空浓缩,产生呈黑色无定形固体状的6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺(530mg,57%)。

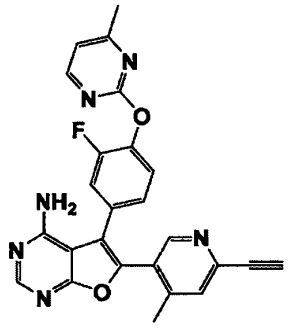
[2085] 6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)呋喃并[2,3-d]嘧啶-4-胺

[2086] 

[2087] 步骤4:向圆底烧瓶中装入6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺(500mg,0.88mmol)、四氢呋喃(10mL)及搅拌棒。添加TBAF(0.88mL,0.88mmol),且在室温下搅拌溶液30分钟。所得粗物质通过硅胶色谱纯化(50g柱;用二氯甲烷/甲醇洗脱;比率=10:1)。真空浓缩产生粗产物。所得粗物质通过制备型HPLC纯化(柱:XBridge Prep OBD C18柱,30×150mm 5um;移动相A:水(10MMOL/LNH_4HCO_3+0.1%$NH_3 \cdot H_2O$),移动相B:ACN;流量:60mL/min;梯度:25B至55B,历时8分钟;220nm;RT1:7.23)。冻干产生呈白色无定形固体状的6-(6-乙炔基-4-甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺(215mg,54%)。

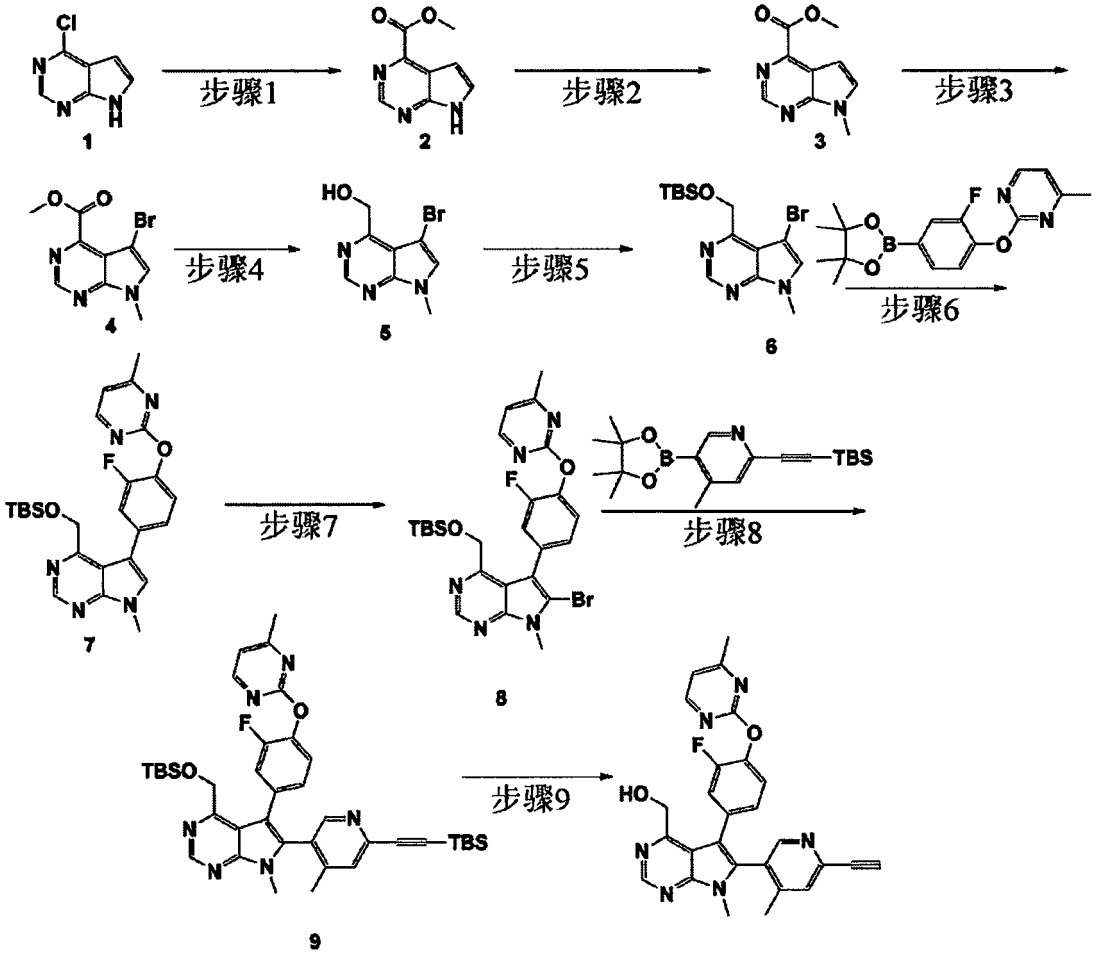
[2088] 表44.示例性化合物

[2089]

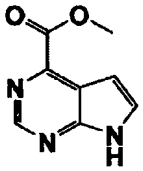
化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}呋喃并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 5.0 Hz, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 7.59 (s, 1H), 7.47 - 7.40 (m, 2H), 7.23 - 7.19 (m, 2H), 4.45 (s, 1H), 2.43 (s, 3H), 2.20 (s, 3H).	453.15

[2090] 实例46

[2091] 流程43

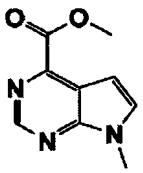
[2092] 

[2093] 7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯

[2094] 

[2095] 步骤1:向压力槽反应器中装入4-氯-7H-吡咯并[2,3-d]嘧啶(30g,195mmol)、TEA(59.1g,585mmol)、[(R)-(+)-2,2′-双(二苯膦基)-1,1′-联萘]氯化钯(II)(1.55g,1.95mmol)、MeOH(500mL)及搅拌棒。在100℃下、在CO气氛(10atm)下搅拌混合物12小时。反应混合物经由硅藻土垫过滤,用EA洗涤垫,且真空浓缩滤液,产生呈黄色无定形固体状的7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯(25.0g,72%)。

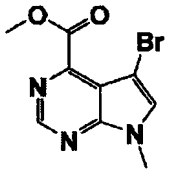
[2096] 7-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯

[2097] 

[2098] 步骤2:向圆底烧瓶中装入7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯(20g,112mmol)、DMF(100mL)及搅拌棒。添加NaH(10.7g,448mmol),且在0℃下搅拌反应混合物30分钟。然后添加MeI(15.8g,112mmol)且在0℃下搅拌溶液1小时。反应混合物用水(500mL)稀释,且水相用EA(100mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗

物质通过硅胶色谱纯化(100g柱;用庚烷/乙酸乙酯洗脱;比率＝3:1)。真空浓缩,产生呈灰白色无定形固体状的7-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯(13.0g,61%)。

[2099] 5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯

[2100] 

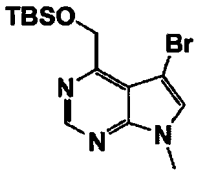
[2101] 步骤3:向圆底烧瓶中装入7-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯(10g,52.3mmol)、DMF(200mL)及搅拌棒。添加NBS(11.1g,62.7mmol),且在室温下搅拌溶液1小时。反应混合物用水(300mL)稀释,且水相用EA(300mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(100g柱;用二氯甲烷/甲醇洗脱;比率＝50:4-17561)。真空浓缩,产生呈灰白色无定形固体状的5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯(10.0g,71%)。

[2102] (5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-基)甲醇

[2103]

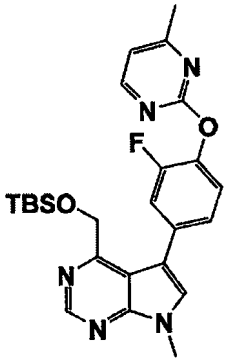
[2104] 步骤4:向圆底烧瓶中装入5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸甲酯(3g,11.1mmol)、THF(50mL)及搅拌棒。在-50℃下添加$LiBH_4$(11.1mL,11.1mmol)。在-50℃下搅拌反应混合物1小时。通过添加2mL EA来淬灭反应。反应混合物用水(100mL)稀释,且水相用DCM(100mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用庚烷/乙酸乙酯洗脱;比率＝1:1)。真空浓缩,产生呈灰白色无定形固体状的{5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-基}甲醇(850mg,32%)。

[2105] 5-溴-4-(((叔丁基二甲基硅烷基)氧基)甲基)-7-甲基-7H-吡咯并[2,3-d]嘧啶

[2106] 

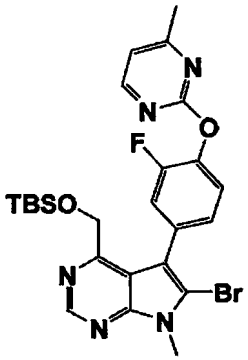
[2107] 步骤5:向圆底烧瓶中装入{5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-基}甲醇(400mg,1.65mmol)、1H-咪唑(561mg,8.25mmol)、THF(10mL)及搅拌棒。添加TBSCl(745mg,4.94mmol),且在室温下搅拌溶液12小时。反应混合物用水(100mL)稀释,且水相用EA(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(20g柱;用庚烷/乙酸乙酯洗脱;比率＝1:1)。真空浓缩,产生呈黄色无定形固体状的5-溴-4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶(330mg,56%)。

[2108] 4-(((叔丁基二甲基硅烷基)氧基)甲基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶

[2109] 

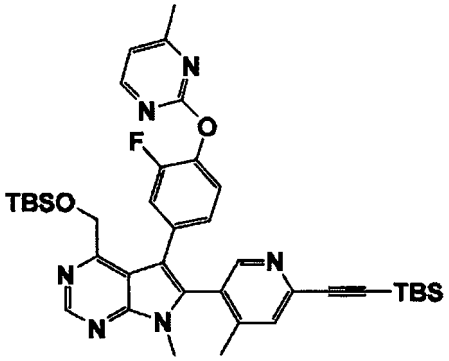
[2110] 步骤6:向可再密封的反应瓶中装入5-溴-4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶(750mg,2.10mmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(832mg,2.52mmol)、K_3PO_4(1.33g,6.30mmol)、Pd(dppf)Cl_2(307mg,0.42mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(20mL),且在90℃下搅拌混合物1小时。反应混合物用水(50mL)稀释,且水相用DCM(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用PE:EA洗脱;比率=1:1)。真空浓缩,产生呈黄色无定形固体状的2-[4-(4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟苯氧基]-4-甲基嘧啶(760mg,75%)。

[2111] 6-溴-4-(((叔丁基二甲基硅烷基)氧基)甲基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶

[2112] 

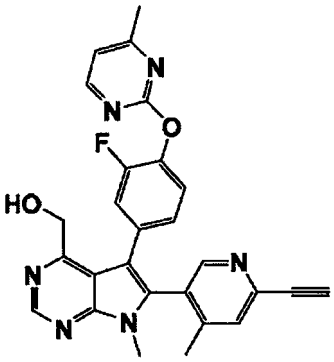
[2113] 步骤7:向圆底烧瓶中装入2-[4-(4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟苯氧基]-4-甲基嘧啶(700mg,1.45mmol)、二甲基甲酰胺(20mL)及搅拌棒。添加DBDMH(331mg,1.16mmol),且在0℃下搅拌溶液2小时。然后用Na2SO3水溶液淬灭反应。反应混合物用水(100mL)稀释,且水相用DCM(100mL)萃取三次。所得粗物质通过制备型TLC(用DCM:MeOH;比率=20:1洗脱)来纯化。真空浓缩,产生呈黑色无定形固体状的2-[4-(6-溴-4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟苯氧基]-4-甲基嘧啶(400mg,49%)。

[2114] 6-(6-((叔丁基二甲基硅烷基)乙炔基)-4-甲基吡啶-3-基)-4-(((叔丁基二甲基硅烷基)氧基)甲基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶

[2115] 

[2116] 步骤8:向可再密封的反应瓶中装入2-[4-(6-溴-4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟苯氧基]-4-甲基嘧啶(350mg,0.63mmol)、2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶(893mg,2.50mmol)、Na_2CO_3(198mg,1.87mmol)、$Pd(PPh_3)_4$(144mg,0.1253mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷/H_2O(20mL),且在90℃下搅拌混合物1小时。反应混合物用水(50mL)稀释,且水相用DCM(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色油状的2-[4-(6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟苯氧基]-4-甲基嘧啶(140mg,31%)。

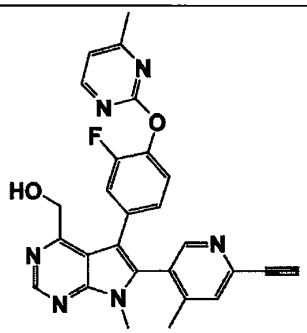
[2117] (6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-基)甲醇

[2118] 

[2119] 步骤9:向圆底烧瓶中装入2-[4-(6-{6-[2-(叔丁基二甲基硅烷基)乙炔基]-4-甲基吡啶-3-基}-4-{[(叔丁基二甲基硅烷基)氧基]甲基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)-2-氟苯氧基]-4-甲基嘧啶(130mg,0.18mmol)、THF(10mL)及搅拌棒。添加TBAF(0.45mL,0.45mmol),且在室温下搅拌溶液30分钟。所得粗物质通过制备型HPLC纯化(柱:XBridge Shield RP18 OBD柱,30*150mm,5um;移动相A:水(10MMOL/L NH_4HCO_3+0.1%$NH_3 \cdot H_2O$),移动相B:ACN;流量:60mL/min;梯度:20B至50B,历时8分钟;254/220nm;RT1:7.28)。冻干产生呈灰白色无定形固体状的[6-(6-乙炔基-4-甲基吡啶-3-基)-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-基]甲醇(39.4mg,46%)。

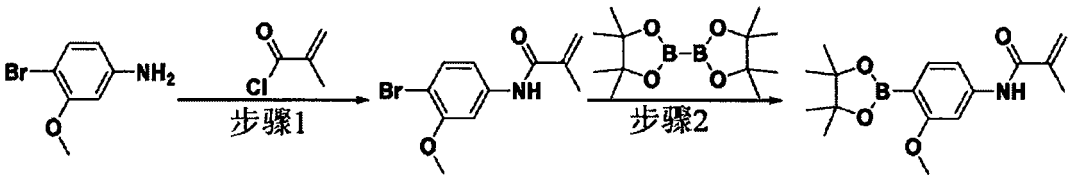
[2120] 表45.示例性化合物

[2121]

化合物	结构	质子 NMR	MS [M+1]
(6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-基)甲醇		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.55 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.59 (s, 1H), 7.37 - 7.27 (m, 2H), 7.19 (d, J = 5.0 Hz, 1H), 7.13 (dd, J = 8.3, 2.2 Hz, 1H), 5.19 (s, 1H), 4.59 - 4.42 (m, 3H), 3.59 (s, 3H), 2.41 (s, 3H), 2.06 (s, 3H).	481.25

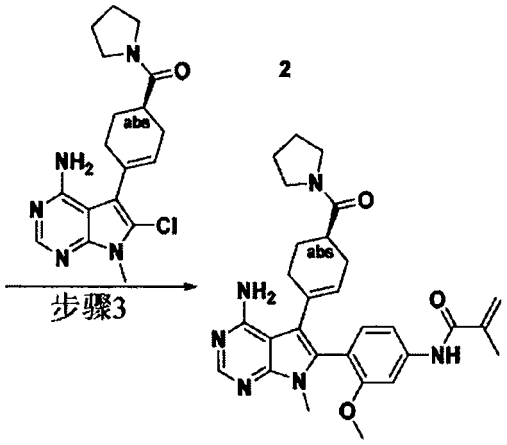
[2122] 实例47

[2123] 流程44



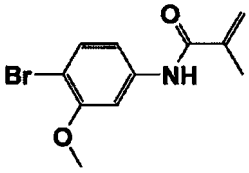
1 2 3

[2124]



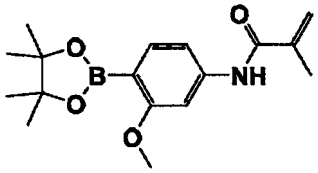
[2125] N-(4-溴-3-甲氧基苯基)-2-甲基丙-2-烯酰胺

[2126]



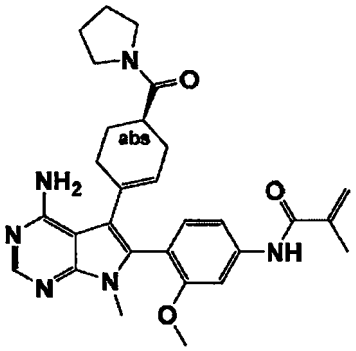
[2127] 步骤1:向圆底烧瓶中装入4-溴-3-甲氧基苯胺(2.9g,14.3mmol)、二氯甲烷(30mL)、TEA(4.33g,42.9mmol)及搅拌棒。添加2-甲基丙-2-烯酰氯(1.64g,15.7mmol),且在0℃下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色固体状的N-(4-溴-3-甲氧基苯基)-2-甲基丙-2-烯酰胺(3.1g,80.3%)。

[2128] N-[3-甲氧基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2-甲基丙-2-烯酰胺

[2129] 

[2130] 步骤2:向可再密封的反应瓶中装入N-(4-溴-3-甲氧基苯基)-2-甲基丙-2-烯酰胺(2.8g,10.3mmol)、4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1,3,2-二氧杂硼杂环戊烷(5.23g,20.6mmol)、Pd(dppf)$_2Cl_2$(753mg,1.03mmol)、AcOK(3.02g,30.9mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷(30mL),且在90℃下搅拌混合物2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色固体状的N-[3-甲氧基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2-甲基丙-2-烯酰胺(2.2g,67.4%)。

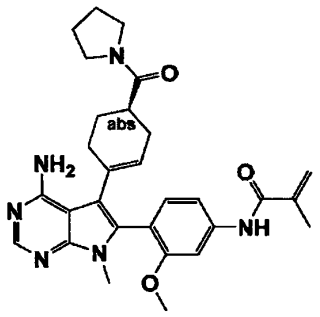
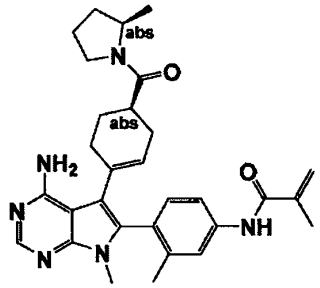
[2131] N-(4-{4-氨基-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-6-基}-3-甲氧基苯基)-2-甲基丙-2-烯酰胺

[2132] 

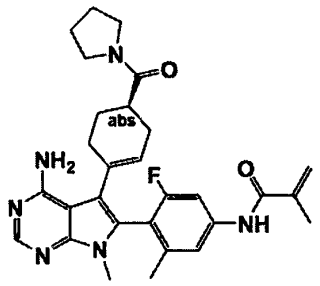
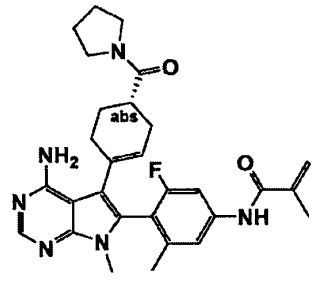
[2133] 步骤3:向可再密封的反应瓶中装入N-[3-甲氧基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2-甲基丙-2-烯酰胺(200mg,630μmol)、6-氯-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺(181mg,504μmol)、XPhos Pd G3(53.3mg,63.0μmol)、XPhos(29.9mg,63.0μmol)、K_3PO_4(398mg,1.88mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(6mL),且在90℃下搅拌混合物2小时。所得粗物质通过制备型HPLC纯化(柱:XBridge Shield RP18 OBD柱,30*150mm,5um;移动相A:水(10MMOL/LNH_4HCO_3+0.1%$NH_3\cdot H_2O$),移动相B:ACN;流量:60mL/min;梯度:25B至50B,历时8分钟;254/220nm;RT1:7.2)。冻干产生呈灰白色无定形固体状的N-(4-{4-氨基-7-甲基-5-[(4R)-4-(吡咯烷-1-羰基)环己-1-烯-1-基]-7H-吡咯并[2,3-d]嘧啶-6-基}-3-甲氧基苯基)-2-甲基丙-2-烯酰胺(70.0mg,27%)。

[2134] 表46.示例性化合物

[2135]

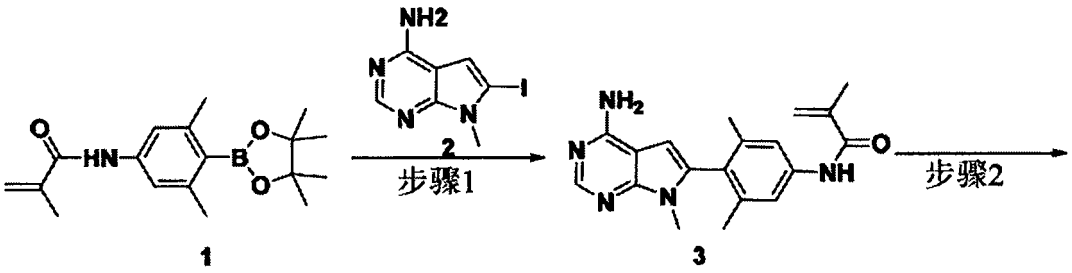
化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲氧基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.08 (d, J = 7.0 Hz, 1H), 7.64 (dd, J = 7.0, 1.9 Hz, 1H), 7.39 (ddd, J = 8.0, 5.9, 1.9 Hz, 1H), 7.15 (dd, J = 8.2, 3.5 Hz, 1H), 6.54 (s, 1H), 6.35 (s, 1H), 5.85 (t, J = 1.1 Hz, 1H), 5.66 (d, J = 22.8 Hz, 1H), 5.56 (s, 1H), 3.76 (d, J = 2.7 Hz, 3H), 3.46 (ddt, J = 18.3, 11.7, 6.1 Hz, 2H), 3.39 (d, J = 3.0 Hz, 3H), 3.31 (s, 2H), 2.84 - 2.64 (m, 1H), 2.42 -2.02 (m, 3H), 1.98 (t, J = 1.3 Hz, 3H), 1.94-1.80(m,3H),1.78-1.68 (m, 3H), 1.64-1.36 (m, 1H).	515.30
N-(4-(4-氨基-7-甲基-5-((R)-4-((R)-2-甲基吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.16 - 8.01 (m, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.62 (dt, J = 8.3, 2.0 Hz, 1H), 7.25 - 7.12 (m, 1H), 6.56 (s, 2H), 5.83 (s, 1H), 5.67 (ddt, J = 17.5, 4.3, 2.2 Hz, 1H), 5.54 (t, J = 1.5 Hz, 1H), 4.10 - 3.93 (m, 1H), 3.46 (td, J = 6.9, 2.5 Hz, 2H), 3.34 (d, J = 2.7 Hz, 3H), 2.80 - 2.64 (m, 1H), 2.38 - 1.97 (t, J = 1.2 Hz, 3H), 1.90 (dddt, J = 10.3, 7.0, 5.3, 3.1 Hz, 3H), 1.83 - 1.70 (m, 2H), 1.67 - 1.41 (m, 3H), 1.15 - 1.00 (m, 3H).	513.35

[2136]

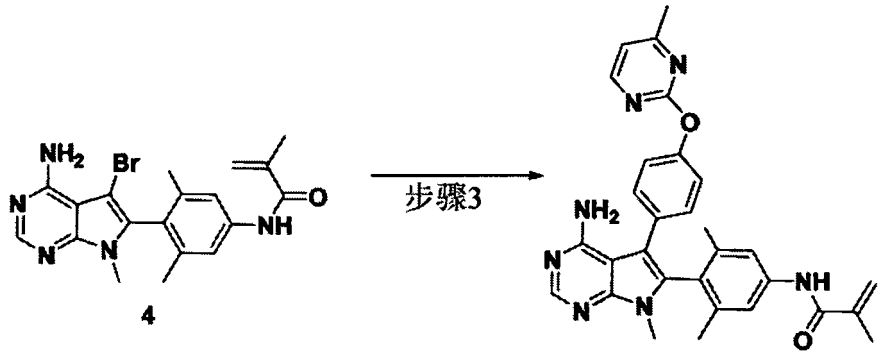
化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟-5-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.13 (d, J = 2.9 Hz, 1H), 7.65 (dt, J = 11.8, 2.1 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 6.68 -6.57 (s, 1H), 5.85 (s, 1H), 5.65 (d, J = 3.9 Hz, 1H), 5.59 (s, 1H), 3.51 - 3.41 (m, 2H), 3.42 (s, 3H), 3.26 (t, J = 6.9 Hz, 2H),2.85-2.78(m,2H) 2.19 (s, 2H), 2.05 (s, 3H), 1.97 (d, J = 1.2 Hz, 5H), 1.86 (p, J = 6.8 Hz, 2H), 1.76 (q, J = 6.7 Hz, 2H), 1.61 (d, J = 4.1 Hz, 2H).	517.30
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3-氟-5-甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ10.04 (s, 1H), 8.12 (d, J = 3.4 Hz, 1H), 7.64 (d, J = 11.6 Hz, 1H), 7.51 (s, 1H), 6.62 (s, 1H), 5.85 (s, 1H), 5.65 (s, 1H), 5.59 (d, J = 1.8 Hz, 1H), 2.75 (s, 1H), 2.19 (s, 2H), 2.05 (s, 3H), 2.00-1.94 (m, 5H), 1.85 (q, J = 6.7 Hz, 2H), 1.76 (q, J = 6.8 Hz, 2H), 1.61 (s, 2H).	517.45

[2137] 实例48

[2138] 流程45

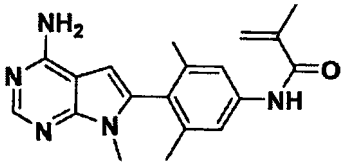


[2139]



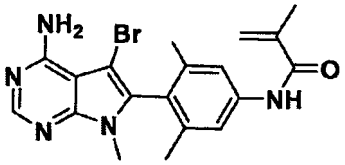
[2140] N-(4-(4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺

[2141]



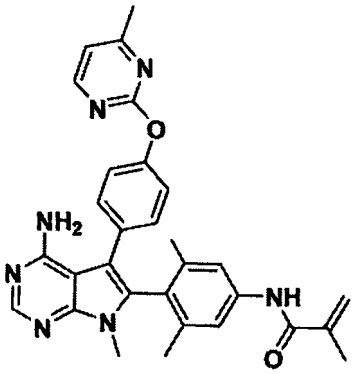
[2142] 步骤1:向可再密封的反应瓶中装入N-[3,5-二甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯基]-2-甲基丙-2-烯酰胺(300mg,951μ.mol)、6-碘-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺(260mg,951μmol)、Pd(AdnBuP)-G2(63.4mg,95.1μmol)、P(AdnBu)HBF4(34.1mg,95.1μmol)、K_3PO_4(604mg,2.85mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷/H2O(10:1,10mL),且在70℃下搅拌混合物12小时。用水稀释混合物,且水相用二氯甲烷(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型TLC(二氯甲烷/甲醇15:1)来纯化。真空浓缩,产生呈黄色固体状的N-(4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3,5-二甲基苯基)-2-甲基丙-2-烯酰胺(180mg,59%)。

[2143] N-(4-(4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺

[2144] 

[2145] 步骤2:向圆底烧瓶中装入N-(4-{4-氨基-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3,5-二甲基苯基)-2-甲基丙-2-烯酰胺(180mg,536μmol)、二甲基甲酰胺(5mL)及搅拌棒。添加NBS(95.4mg,536μmol),且在室温下搅拌溶液0.5小时。混合物用$NaHSO_3$水溶液淬灭且用DCM(3*20mL)萃取。合并有机相且浓缩。所得粗物质通过制备型TLC(DCM/MeOH=15:1)来纯化,产生呈棕色固体状的N-(4-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3,5-二甲基苯基)-2-甲基丙-2-烯酰胺(160mg,72%)。

[2146] N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺

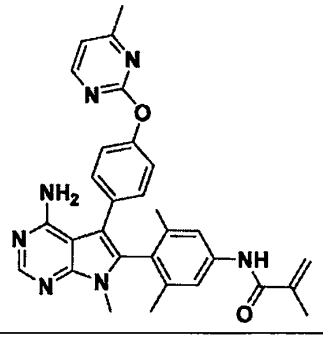
[2147] 

[2148] 步骤3:向可再密封的反应瓶中装入N-(4-{4-氨基-5-溴-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}-3,5-二甲基苯基)-2-甲基丙-2-烯酰胺(150mg,362μmol)、4-甲基-2-[4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]嘧啶(113mg,362μmol)、Pd(dppf)Cl_2(26.4mg,36.2μmol)、K_3PO_4(228mg,1.08mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(8mL),且在90℃下搅拌混合物1小时。反应混合物用水(50mL)稀释,且水相用EtOAc(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(柱:YMC-Actus Triart C18,30*250,5um;移动相A:未定义,移动相B:未定义;流量:50mL/min;梯度:45B至70B,历时8分钟;220nm;RT1:7.23)。冻干产生呈白色无定

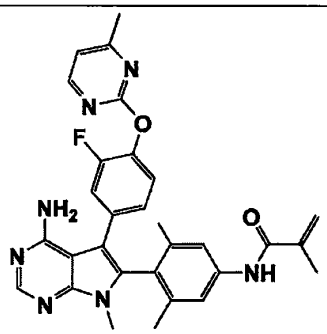
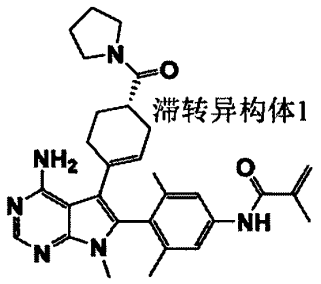
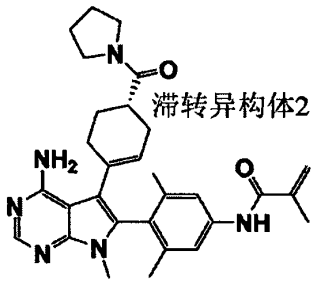
形固体状的N-[4-(4-氨基-7-甲基-5-{4-[(4-甲基嘧啶-2-基)氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基]-2-甲基丙-2-烯酰胺(18.2mg,10%)。

[2149] 表47.示例性化合物

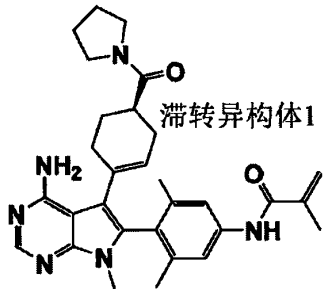
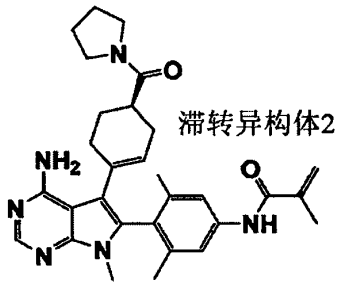
[2150]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-7-甲基-5-(4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.50 (s, 2H), 7.28 - 7.10 (m, 5H), 5.80 (m, 2H), 5.52 (s, 1H), 3.37 (s, 3H), 2.40 (s, 3H), 1.96 (m, 9H).	520.40

[2151]

化合物	结构	质子 NMR	MS [M+1]
N-(4-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.25 - 8.09 (m, 1H), 7.57 - 7.41 (m, 2H), 7.36 - 6.94 (m, 4H), 6.02 - 5.62 (m, 1H), 5.43 (s, 1H), 5.34 (t, J = 1.6 Hz, 1H), 3.78 (s, 3H), 2.42 (s, 3H), 2.10 (s, 3H), 1.85 (s, 3H), 1.78 (d, J = 1.2 Hz, 3H).	538.30
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 5.8 Hz, 1H), 8.14 (d, J = 1.9 Hz, 1H), 7.74 (dd, J = 18.2, 10.8 Hz, 1H), 7.10 (d, J = 6.0 Hz, 1H), 5.84 - 5.74 (m, 1H), 5.65 (s, 1H), 5.54 - 5.47 (m, 1H), 3.76 (s, 3H), 3.59 - 3.43 (m, 2H), 2.78 - 2.62 (m, 1H), 2.37 - 2.14 (m, 3H), 2.10 - 1.99 (m, 9H), 1.99 - 1.91 (m, 5H), 1.88 (d, J = 14.7 Hz, 2H), 1.79 (p, J = 6.7 Hz, 1H), 1.24 (s, 1H).	513.40
(S)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.13 (s, 1H), 7.72 (d, J = 9.4 Hz, 1H), 7.08 (d, J = 1.3 Hz, 1H), 5.80 (d, J = 16.7 Hz, 1H), 5.76 (s, 1H), 5.66 (d, J = 23.7 Hz, 1H), 5.53 - 5.49 (m, 1H), 3.76 (s, 3H), 3.48 (dt, J = 24.2, 8.0 Hz, 2H), 3.17 (d, J = 5.2 Hz, 1H), 2.77 - 2.63 (m, 1H), 2.30 (d, J = 26.8 Hz, 3H), 2.08 (s, 2H), 2.01 (d, J = 6.9 Hz, 8H), 1.96 (d, J = 10.0 Hz, 5H), 1.92 - 1.81 (m, 2H), 1.78 (q, J = 6.7 Hz, 1H), 1.29 - 1.15 (m, 1H).	513.40

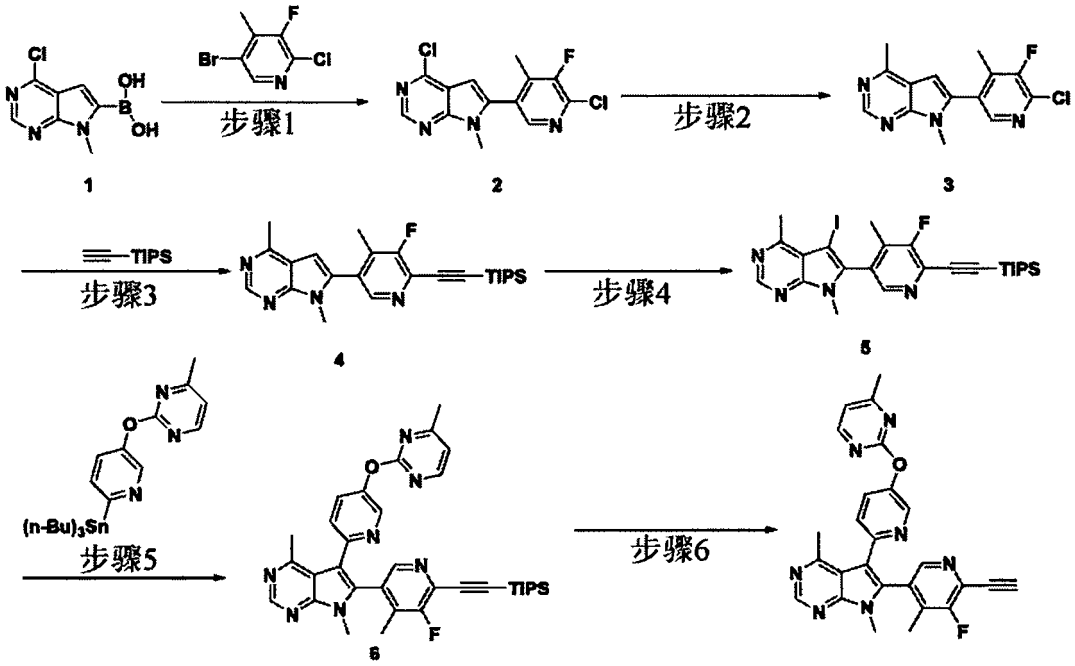
[2152]

化合物	结构	质子 NMR	MS [M+1]
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 6.1 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.72 (d, J = 16.7 Hz, 1H), 7.08 (d, J = 6.0 Hz, 1H), 5.78 (t, J = 10.2 Hz, 1H), 5.65 (s, 1H), 5.51 (dt, J = 6.3, 1.5 Hz, 1H), 3.76 (s, 3H), 3.53 - 3.41 (m, 2H), 3.30 - 3.28 (m, 1H), 2.80 - 2.61 (m, 1H), 2.36 - 2.21 (m, 3H), 2.08 (s, 1H), 2.05 - 2.00 (m, 5H), 1.98 - 1.95 (m, 3H), 1.89 (q, J = 7.3, 6.8 Hz, 4H), 1.78 (q, J = 6.7 Hz, 2H), 1.67 (d, J = 8.6 Hz, 1H), 1.28 - 1.15 (m, 1H).	513.35
(R)-N-(4-(4-氨基-7-甲基-5-(4-(吡咯烷-1-羰基)环己-1-烯-1-基)-7H-吡咯并[2,3-d]嘧啶-6-基)-3,5-二甲基苯基)甲基丙烯酰胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 2.4 Hz, 1H), 8.13 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 1.4 Hz, 1H), 5.82 (s, 1H), 5.77 (d, J = 6.7 Hz, 1H), 5.69 (s, 1H), 5.63 (s, 1H), 5.51 (d, J = 7.0 Hz, 1H), 3.76 (s, 3H), 3.57 - 3.38 (m, 3H), 2.76 (s, 1H), 2.67 (d, J = 1.9 Hz,1H), 2.34 - 2.23 (m, 2H), 2.12 (s, 1H), 2.08 (s, 1H), 2.02 (s, 5H), 2.01 - 1.97 (m, 3H), 1.95 (s, 5H), 1.89 (d, J = 14.7 Hz, 2H), 1.79 (p, J = 6.7 Hz, 1H), 1.24 (s, 2H).	513.35

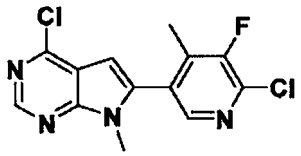
[2153] 实例49

[2154] 流程46

[2155]

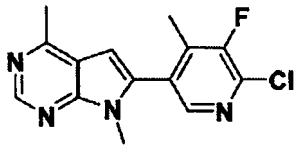


[2156] 4-氯-6-(6-氯-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶

[2157] 

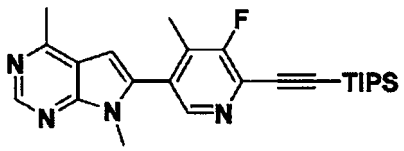
[2158] 步骤1:向可再密封的反应瓶中装入(4-氯-7-甲基-7H-吡咯并[2,3-d]嘧啶-6-基)硼酸(2g,9.48mmol)、5-溴-2-氯-3-氟-4-甲基吡啶(2.3g,10.4mmol)、$Pd(dtbpf)Cl_2$(617mg,0.948μmol)、K_3PO_4(6g,28.44mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷:水=5:1(40mL),且在70℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。真空蒸发,残余物通过硅胶柱色谱(用PE/EA(30:1至1:1)洗脱)来纯化,得到呈黄色无定形固体状的4-氯-6-(6-氯-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶(1.3g,44%)。

[2159] 6-(6-氯-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[2160] 

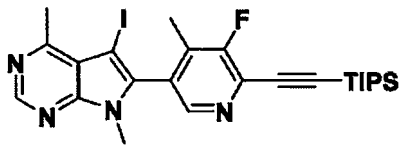
[2161] 步骤2:向可再密封的反应瓶中装入4-氯-6-(6-氯-5-氟-4-甲基吡啶-3-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶(1.28g,4.13mmol)、$Pd(PPh_3)_4$(478mg,0.413mmol)、DMF(20mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加$Zn(CH_3)_2$(2M,1.4mL),且在90℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。残余物通过硅胶柱色谱(用PE/EA(30:1至1:2)洗脱)来纯化,得到呈黄色无定形固体状的6-(6-氯-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(420mg,68%)。

[2162] 6-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[2163] 

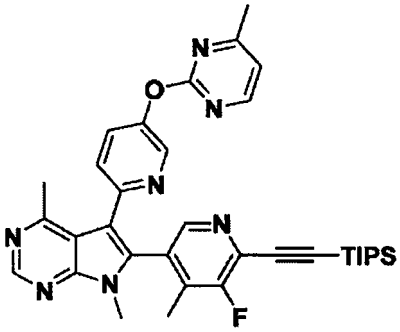
[2164] 步骤3:向可再密封的反应瓶中装入6-(6-氯-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(1.28g,4.13mmol)、$Pd(PPh_3)_2Cl_2$(580mg,0.826mmol)、CuI(313mg,1.65mmol)、乙炔基三异丙基硅烷(526mg,2.89mmol)、TEA(1.25g,12.39mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF(20mL),且在90℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得混合物经由C18柱纯化。真空浓缩,产生呈黄色无定形固体状的6-(6-氯-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(720mg,40%)。

[2165] 6-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-5-碘-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶

[2166] 

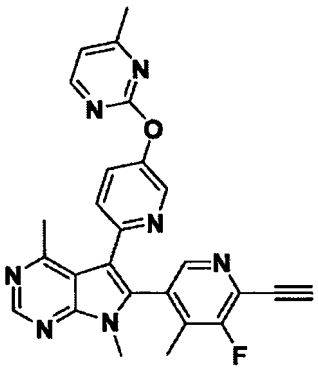
[2167] 步骤4:向圆底烧瓶中装入6-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(400mg,1.60mmol)、DCM(8mL),添加TFA(547mg,4.8mmol)及搅拌棒。添加NIS(396mg,1.76mmol),且在室温下搅拌溶液1小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过硅胶色谱纯化。真空浓缩,产生呈黄色无定形固体状的46-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-5-碘-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(760mg,85%)。

[2168] 6-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-4,7-二甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶

[2169] 

[2170] 步骤5:向圆底烧瓶中装入6-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-5-碘-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶(740mg,1.32mmol)、4-甲基-2-((6-(三丁基锡烷基)吡啶-3-基)氧基)嘧啶(1.26g,2.64mmol)、$Pd(PPh_3)_4$(153mg,0.132mmol)、CuI(50mg,0.264μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF(15mL),且在90℃下搅拌溶液2小时。使反应混合物处于真空中。所得粗物质通过制备型TLC纯化。真空浓缩,产生呈黄色无定形固体状的6-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-4,7-二甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶(540mg,66%)。

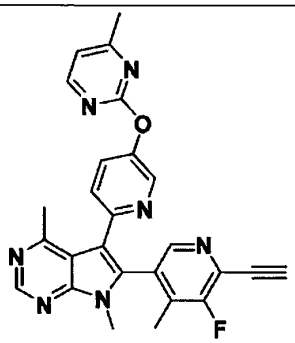
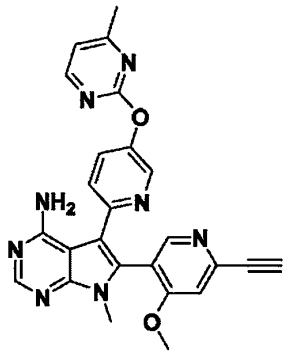
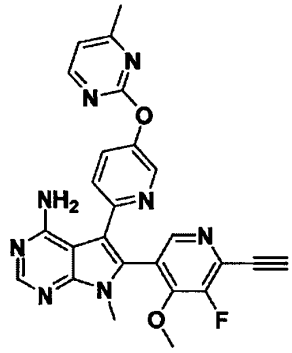
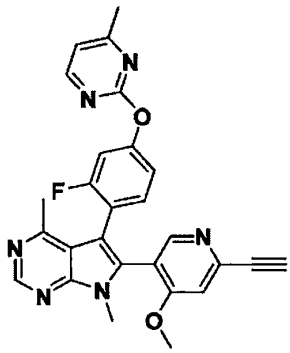
[2171] 6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶

[2172] 

[2173] 步骤6:向圆底烧瓶中装入6-(5-氟-4-甲基-6-((三异丙基硅烷基)乙炔基)吡啶-3-基)-4,7-二甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶(520mg,0.84mmol)、THF(8mL)及搅拌棒。添加TBAF(1mL,1mmol),且在室温下搅拌溶液1小时。反应混合物用水稀释,用DCM萃取,经Na_2SO_4干燥,真空浓缩。残余物通过制备型HPLC纯化(柱:XBridge Shield RP18 OBD柱,30*150mm,5um;移动相A:水(10MMOL/LNH_4HCO_3+0.1%$NH_3 \cdot H_2O$),移动相B:ACN;流量:60mL/min;梯度:20B至45B,历时8分钟;254/220nm;RT1:

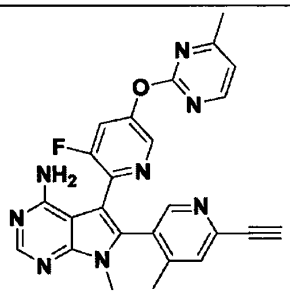
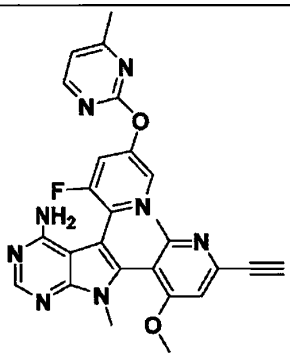
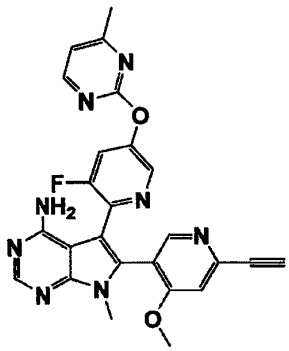
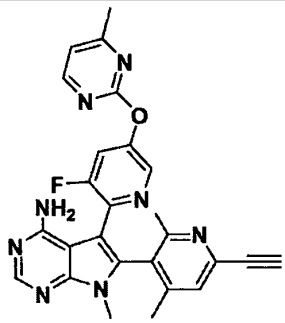
7.77)。冻干产生呈白色无定形固体状的6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶(213.2mg,55%)。

[2174] 表48.示例性化合物

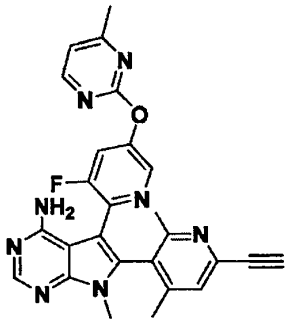
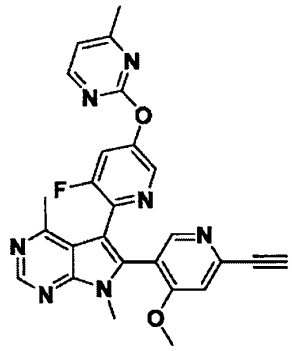
化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-5-氟-4-甲基吡啶-3-基)-4,7-二甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶		1H NMR (400 MHz, DMSO-d6) δ 8.81 (s, 1H), 8.54 (d, J = 2.7 Hz, 1H), 8.50 (d, J = 5.0 Hz, 1H), 8.43 (s, 1H), 7.61 (dd, J = 8.5, 2.8 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 5.0 Hz, 1H), 4.82 (d, J = 0.8 Hz, 1H), 3.63 (s, 3H), 2.40 (s, 3H), 1.98 (d, J = 2.1 Hz, 3H).	446.15
6-(6-乙炔基-4-甲氧基吡啶-3-基)-7-甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 2.8 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 7.56 - 7.49 (m, 1H), 7.51 (s, 1H), 7.19 (d, J = 5.0 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 4.49 (s, 1H), 3.89 (s, 3H), 3.48 (s, 3H), 2.42 (s, 3H).	465.20
6-(6-乙炔基-5-氟-4-甲氧基吡啶-3-基)-7-甲基-5-(5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d6) δ 8.59 (d, J = 2.9 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 7.61 (dd, J = 8.8, 2.8 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 7.20 (d, J = 5.0 Hz, 1H), 5.60 (d, J = 0.9 Hz, 1H), 3.75 (s, 3H), 3.52 (s, 3H), 2.43 (s, 3H).	483.15
6-(6-乙炔基-4-甲氧基吡啶-3-基)-5-(2-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.50 (d, J = 5.0 Hz, 1H), 8.23 (d, J = 97.8 Hz, 1H), 7.46 (d, J = 19.1 Hz, 1H), 7.38 (s, 1H), 7.33 - 6.95 (m, 3H), 4.47 (d, J = 3.7 Hz, 1H), 3.91 (s, 3H), 3.64 (d, J = 9.7 Hz, 3H), 2.42 (s, 3H), 2.38 (s, 3H).	481.15

[2175]

[2176]

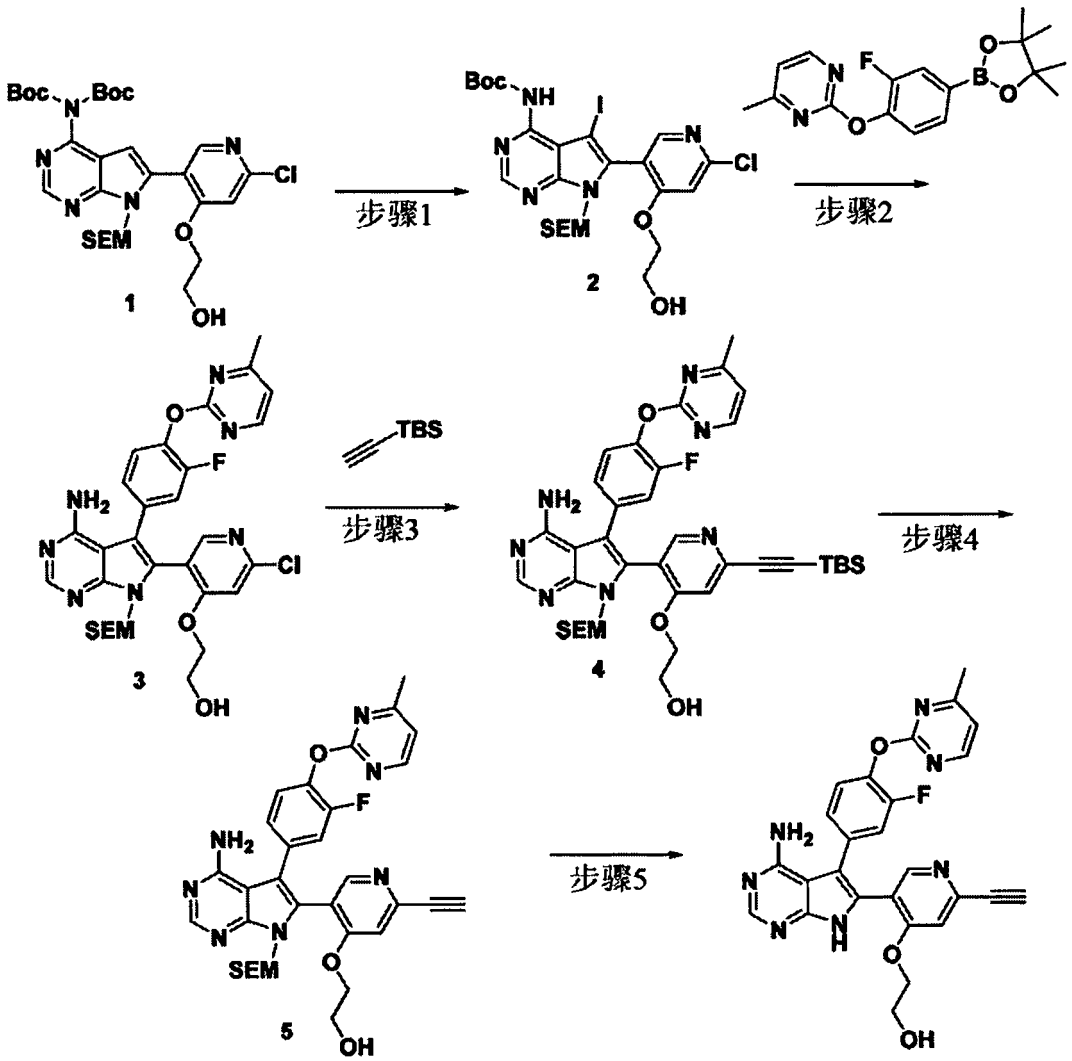
化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-4-甲基吡啶-3-基)-5-(3-氟-5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 - 8.56 (m, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.36 (s, 1H), 8.28 (s, 1H), 7.77 (dd, J = 11.0, 2.3 Hz, 1H), 7.61 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 7.02 (s, 1H), 4.42 (s, 1H), 3.52 (s, 3H), 2.43 (s, 3H), 2.05 (s, 3H).	467.30
6-(6-乙炔基-4-甲氧基-2-甲基吡啶-3-基)-5-(3-氟-5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.53 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.76 (dd, J = 11.0, 2.3 Hz, 1H), 7.30 (s, 1H), 7.23 (d, J = 5.0 Hz, 1H), 6.87 (s, 1H), 4.41 (s, 1H), 3.84 (s, 3H), 3.46 (s, 3H), 2.43 (s, 3H), 1.92 (s, 3H), 1.24 (s, 1H).	497.20
6-(6-乙炔基-4-甲氧基吡啶-3-基)-5-(3-氟-5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 2.3 Hz, 1H), 8.53 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.80 - 7.72 (m, 1H), 7.45 (s, 1H), 7.24 (d, J = 5.0 Hz, 1H), 7.01 - 6.96 (m, 1H), 4.47 (s, 1H), 3.88 (s, 3H), 3.56 (s, 3H), 2.44 (s, 3H).	483.20
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺 **滞转异构体 1**		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (dd, J = 2.3, 0.9 Hz, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.78 (dd, J = 11.0, 2.3 Hz, 1H), 7.43 (s, 1H), 7.23 (d, J = 5.0 Hz, 1H), 6.81 (s, 2H), 4.37 (s, 1H), 3.44 (s, 3H), 2.42 (s, 3H), 2.13 (s, 3H), 1.97 (s, 3H).	491.20

[2177]

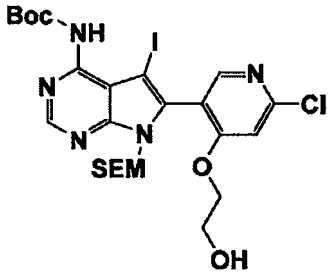
化合物	结构	质子 NMR	MS [M+1]
6-(6-乙炔基-2,4-二甲基吡啶-3-基)-5-(3-氟-5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-7-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	 滞转异构体 2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 2.2 Hz, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.78 (dd, J = 11.0, 2.3 Hz, 1H), 7.43 (s, 1H), 7.22 (s, 1H), 6.81 (s, 2H), 4.37 (d, J = 0.8 Hz, 1H), 3.44 (s, 3H), 2.42 (s, 3H), 2.13 (s, 3H), 1.97 (s, 3H).	481.20
6-(6-乙炔基-4-甲氧基吡啶-3-基)-5-(3-氟-5-((4-甲基嘧啶-2-基)氧基)吡啶-2-基)-4,7-二甲基-7H-吡咯并[2,3-d]嘧啶		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.53 (d, J = 5.0 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.19 (s, 1H), 7.86 (dd, J = 10.3, 2.3 Hz, 1H), 7.41 (s, 1H), 7.24 (d, J = 5.1 Hz, 1H), 4.47 (s, 1H), 3.84 (s, 3H), 3.68 (s, 3H), 2.42 (d, J = 11.5 Hz, 6H).	482.10

[2178] 实例50

[2179] 流程47

[2180] 

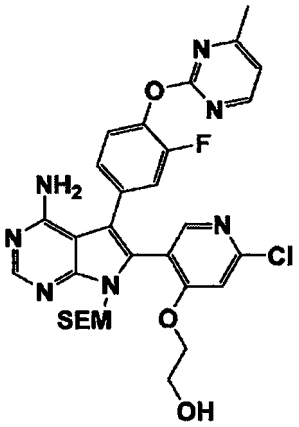
[2181] (6-(6-氯-4-(2-羟基乙氧基)吡啶-3-基)-5-碘-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-4-基)氨基甲酸叔丁酯

[2182] 

[2183] 步骤1:向圆底烧瓶中装入N-[(叔丁氧基)羰基]-N-{6-[6-氯-4-(2-羟基乙氧基)吡啶-3-基]-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-基}氨基甲酸叔丁酯(3g,4.71mmol)、TFA(2.27g,23.5mmol)、二氯甲烷(40mL)及搅拌棒。添加NIS(1.27g,5.65mmol),且在室温下搅拌溶液1小时。反应混合物用水(40mL)稀释,且水相用二氯甲烷(60mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过flash来纯化(乙腈/水),真空浓缩,产生呈黄色无定形固体状的(6-(6-氯-4-(2-羟基乙氧基)吡啶-3-基)-5-碘-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-4-基)氨基甲酸叔丁酯(600mg)及N-[(叔丁氧基)羰基]-N-{6-[6-氯-4-(2-羟基乙氧基)吡啶-3-基]-5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-

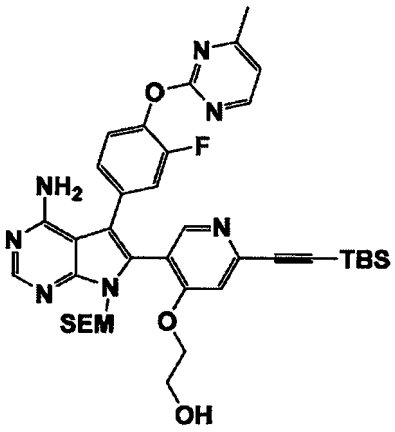
基}氨基甲酸叔丁酯(3.00g,83%)。

[2184] 2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基)氧基)乙-1-醇

[2185] 

[2186] 步骤2:向可再密封的反应瓶中装入N-{6-[6-氯-4-(2-羟基乙氧基)吡啶-3-基]-5-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-基}氨基甲酸叔丁酯(500mg,755μmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(299mg,906μmol)、K_3PO_4(479mg,2.26mmol)、Pd(dppf)Cl_2(55.2mg,75.5μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(10mL),且在90℃下搅拌混合物1小时。反应混合物用水(20mL)稀释,且水相用EA(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(10g柱;用二氯甲烷/甲醇洗脱;比率=15:1)。真空浓缩,产生呈黄色无定形固体状的2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基)氧基)乙-1-醇(320mg,66%)。

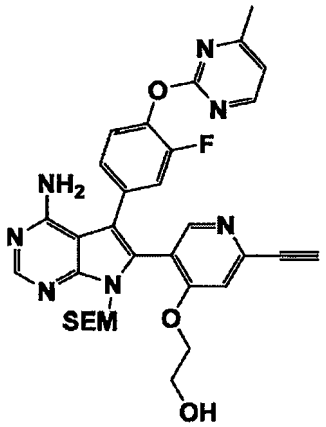
[2187] 2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-((叔丁基二甲基硅烷基)乙炔基)吡啶-4-基)氧基)乙-1-醇

[2188] 

[2189] 步骤3:向可再密封的反应瓶中装入2-{[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基]氧基}乙-1-醇(280mg,438μmol)、叔丁基(乙炔基)二甲基硅烷(122mg,876μmol)、CuI(33.2mg,175μmol)、TEA(132mg,1.31mmol)、Pd(dppf)Cl_2(64.1mg,87.6μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DMF(5mL),且在50℃下搅拌混合物2小时。反应混

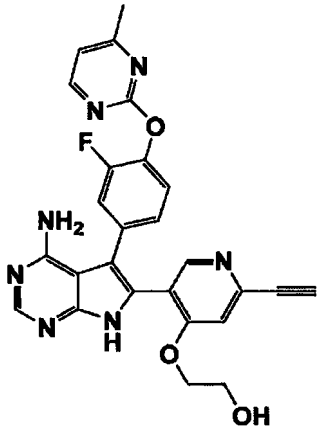
合物用水(20mL)稀释,且水相用EA(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过flash来纯化(乙腈/水)。真空浓缩,产生呈灰白色无定形固体状的2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-((叔丁基二甲基硅烷基)乙炔基)吡啶-4-基)氧基)乙-1-醇(110mg,34%)。

[2190] 2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)氧基)乙-1-醇

[2191] 

[2192] 步骤4:向圆底烧瓶中装入2-{[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-[2-(叔丁基二甲基硅烷基)乙炔基]吡啶-4基]氧基}乙-1-醇(100mg,134μmol)、THF(5mL)及搅拌棒。添加TBAF(35.0mg,134μmol),且在室温下搅拌溶液30分钟。所得粗物质通过硅胶色谱纯化(5g柱;用二氯甲烷/甲醇洗脱;比率=10:1)。真空浓缩,产生呈棕色无定形固体状的2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)氧基)乙-1-醇(80.0mg,95%)。

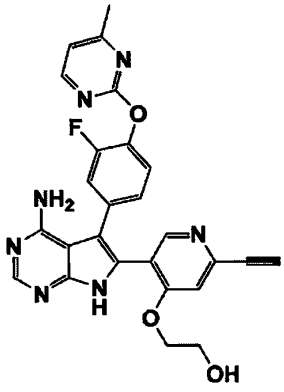
[2193] 2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)氧基)乙-1-醇

[2194] 

[2195] 步骤5:向圆底烧瓶中装入2-{[5-(4-氨基-5-{3-氟-4-[(4-甲基嘧啶-2-基)氧基]苯基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基]氧基}乙-1-醇(70mg,111μmol)及搅拌棒。添加CH_3SO_3H/MeOH(1:2,2mL),且在70℃下搅拌溶液1小时,且然后用TEA将溶液pH值调节至7。所得粗物质通过硅胶色谱(5g柱;用二氯甲烷/甲醇洗脱;比率=10:1)纯化,真空浓缩。所得粗物质通过HPLC纯化(柱:YMC-Actus

Triart C18,30*250,5um;移动相A:水(10MMOL/L NH_4HCO_3),移动相B:ACN;流量:60mL/min;梯度:15B至48B,历时7分钟;254/220nm;RT1:6.48)。冻干产生呈灰白色无定形固体状的2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)氧基)乙-1-醇(9.20mg,17%)。

[2196] 表49.示例性化合物

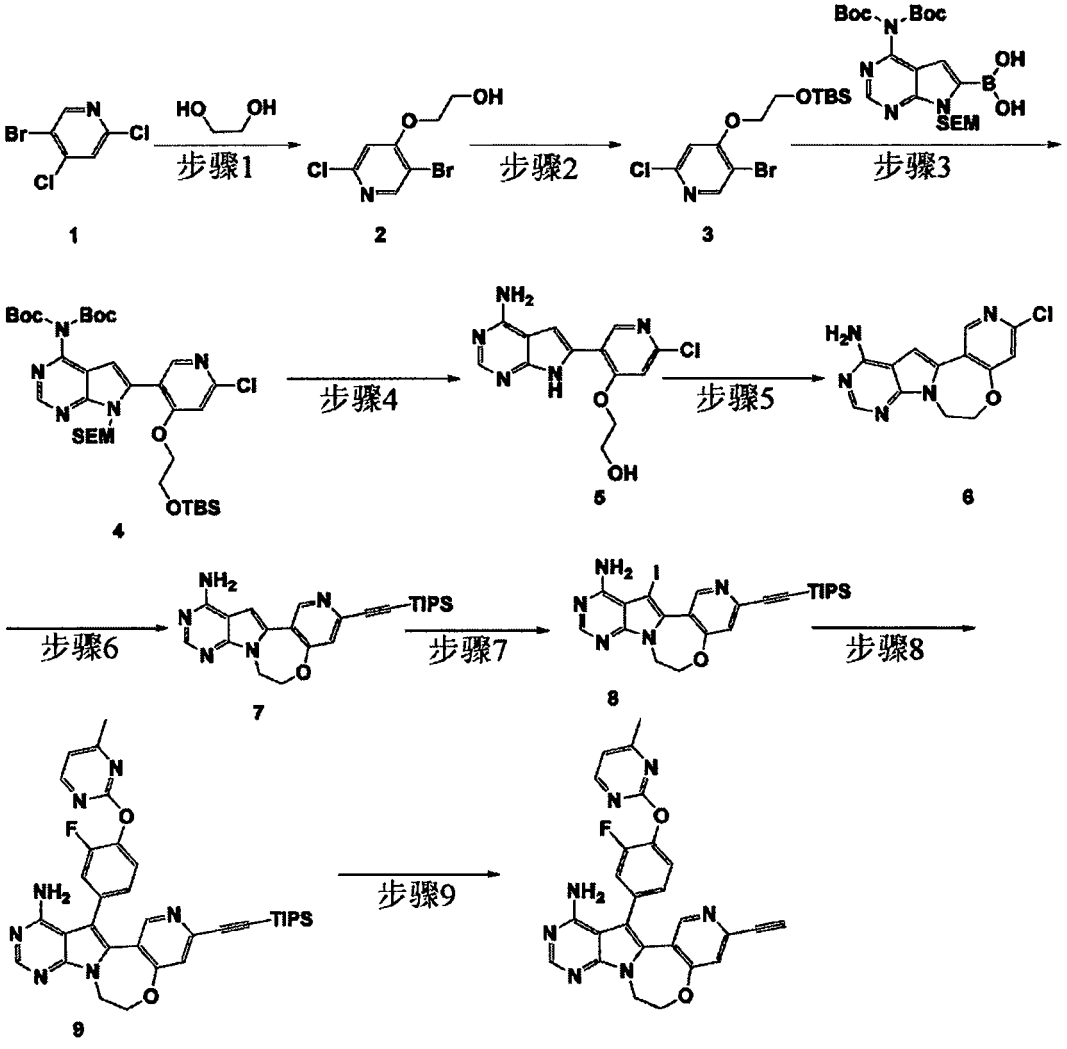
化合物	结构	质子 NMR	MS [M+1]
2-((5-(4-氨基-5-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7H-吡咯并[2,3-d]嘧啶-6-基)-2-乙炔基吡啶-4-基)氧基)乙-1-醇		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.40 - 7.30 (m, 2H), 7.27 - 7.17 (m, 2H), 7.10 (dd, J = 8.2, 2.0 Hz, 1H), 6.06 (s, 1H), 4.87 (t, J = 5.4 Hz, 1H), 4.40 (s, 1H), 4.01 (t, J = 4.9 Hz, 2H), 3.56 (q, J = 5.1 Hz, 2H), 2.43 (s, 3H).	498.30

[2197]

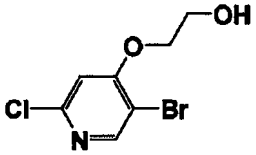
[2198] 实例51

[2199] 流程48

[2200]

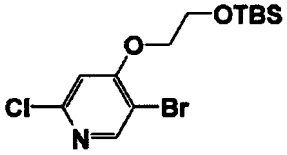


[2201] 2-((5-溴-2-氯吡啶-4-基)氧基)乙-1-醇

[2202] 

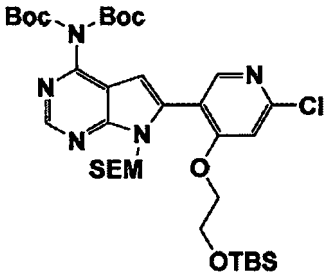
[2203] 步骤1:向圆底烧瓶中装入乙烷-1,2-二醇(81.9g,1.32mol)、DMSO(800mL)及搅拌棒。添加NaH(7.58g,316mmol),且在室温下搅拌溶液30分钟,且然后添加5-溴-2,4-二氯吡啶(60g,264mmol),且在50℃下搅拌溶液1小时。反应混合物用水(500mL)稀释,且水相用EA(500mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(500g柱;用DCM/EA洗脱;比率=1:1)。真空浓缩,产生呈黄色油状的2-[(5-溴-2-氯吡啶-4-基)氧基]乙-1-醇(55.0g,82%)。

[2204] 5-溴-4-(2-((叔丁基二甲基硅烷基)氧基)乙氧基)-2-氯吡啶

[2205] 

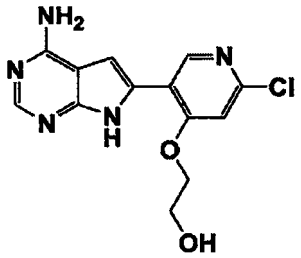
[2206] 步骤2:向圆底烧瓶中装入2-[(5-溴-2-氯吡啶-4-基)氧基]乙-1-醇(55g,217mmol)、咪唑(73.5g,1.08mol)、DMF(1000mL)及搅拌棒。添加TBSCl(65.4g,434mmol),且在室温下搅拌溶液16小时。反应混合物用EA(1000mL)萃取,合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(600g柱;用PE/EA洗脱;比率=40:1)。真空浓缩,产生呈灰白色结晶固体状的5-溴-4-(2-((叔丁基二甲基硅烷基)氧基)乙氧基)-2-氯吡啶(82.4g,100%)。

[2207] N-[(叔丁氧基)羰基]-N-[6-(4-{2-[(叔丁基二甲基硅烷基)氧基]乙氧基}-6-氯吡啶-3-基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-基]氨基甲酸叔丁酯

[2208] 

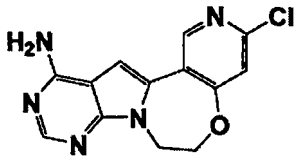
[2209] 步骤3:向可再密封的反应瓶中装入5-溴-4-{2-[(叔丁基二甲基硅烷基)氧基]乙氧基}-2-氯吡啶(28g,76.3mmol)、(4-{双[(叔丁氧基)羰基]氨基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)硼酸(77.2g,152mmol)、CsF(34.6g,228mmol)、Pd(dtbpf)Cl_2(4.97g,7.63mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷/H_2O(600mL),且在70℃下搅拌混合物2小时。反应混合物用水(400mL)稀释,且水相用DCM(500mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过flash来纯化(乙腈/水)。真空浓缩,产生呈黄色无定形固体状的N-[(叔丁氧基)羰基]-N-[6-(4-{2-[(叔丁基二甲基硅烷基)氧基]乙氧基}-6-氯吡啶-3-基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-基]氨基甲酸叔丁酯(30.0g,52%)。

[2210] 2-((5-(4-氨基-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基)氧基)乙-1-醇

[2211] 

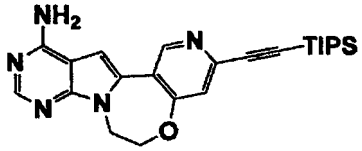
[2212] 步骤4:向圆底烧瓶中装入N-[(叔丁氧基)羰基]-N-[6-(4-{2-[(叔丁基二甲基硅烷基)氧基]乙氧基}-6-氯吡啶-3-基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-基]氨基甲酸叔丁酯(29g,38.6mmol)及搅拌棒。添加HCl(12M)/MeOH(1:1,600mL),且在室温下搅拌溶液3小时,且然后在0℃下用TEA将溶液pH值调节至8,然后真空浓缩。沉淀的固体通过过滤收集且用ACN(300mL)洗涤三次,真空干燥,产生呈灰白色无定形固体状的2-((5-(4-氨基-7H-吡咯并[2,3-d]嘧啶-6-基)-2-氯吡啶-4-基)氧基)乙-1-醇(8.00g,67%)。

[2213] 3-氯-6,7-二氢吡啶并[3,4-F]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺

[2214] 

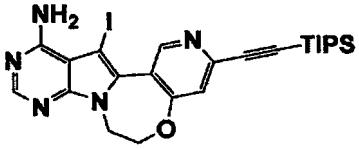
[2215] 步骤5:向可再密封的反应瓶中装入2-[(5-{4-氨基-7H-吡咯并[2,3-d]嘧啶-6-基}-2-氯吡啶-4-基)氧基]乙-1-醇(7.9g,25.8mmol)、DIAD(10.4g,51.6mmol)、THF(80mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加含PPh_3(13.5g,51.6mmol)的THF(40ml),且在30℃下搅拌混合物3小时。在真空中移除溶剂。残余物用DCM(200mL)洗涤,真空干燥,产生呈灰白色无定形固体状的3-氯-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(5.00g,67%)。

[2216] 3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺

[2217] 

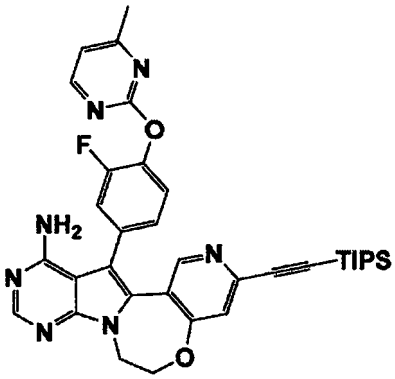
[2218] 步骤6:向可再密封的反应瓶中装入3-氯-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(4.9g,17.0mmol)、DMF(150mL)、TEA(5.15g,50.9mmol)、CuI(1.29g,6.80mmol)、Pd(dppf)Cl_2.CH_2Cl_2(2.77g,3.40mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。然后添加乙炔基参(丙-2-基)硅烷(6.20g,34.0mmol),且在70℃下搅拌混合物2小时。反应混合物用水(500mL)稀释,且水相用二氯甲烷(400mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(100g柱;用二氯甲烷/甲醇洗脱;比率=20:1)。真空浓缩,产生呈棕色无定形固体状的3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(4.5g,61.0%)。

[2219] 13-碘-3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺

[2220] 

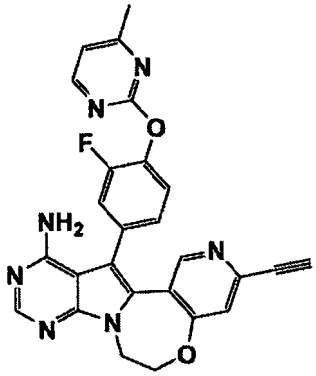
[2221] 步骤7:向圆底烧瓶中装入3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(4.4g,10.1mmol)、TFA(3.45g,30.3mmol)及搅拌棒。添加二氯甲烷(100mL),且然后在0℃下添加NIS(3.39g,15.1mmol),且在室温下搅拌溶液1小时。反应物用$NaHSO_3$水溶液淬灭,然后用碳酸氢钠将PH调节至6-7。反应混合物用水(30mL)稀释,沉淀的固体通过过滤收集且用ACN(300mL)洗涤。真空干燥,产生呈灰白色无定形固体状的13-碘-3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(5.50g,97%)。

[2222] 13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺

[2223] 

[2224] 步骤8:向可再密封的反应瓶中装入13-碘-3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(5.4g,9.65mmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(4.75g,14.4mmol)、K_3PO_4(6.13g,28.9mmol)、Pd(dppf)Cl_2.CH_2Cl_2(787mg,965μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(100mL),且在90℃下搅拌混合物1小时。反应混合物用水(80mL)稀释,且水相用二氯甲烷(100mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(100g柱;用二氯甲烷/甲醇洗脱;比率=20:1)。真空浓缩,产生呈棕色无定形固体状的13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(4.70g,76%)。

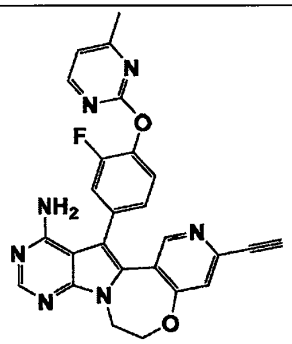
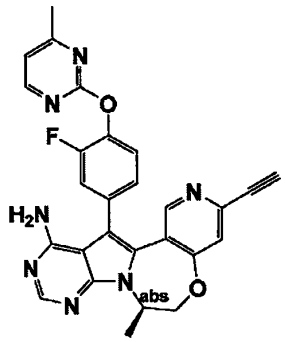
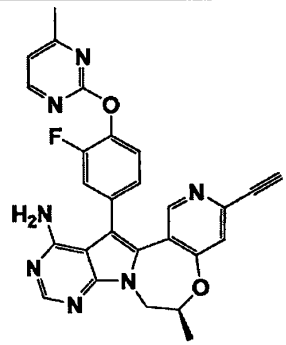
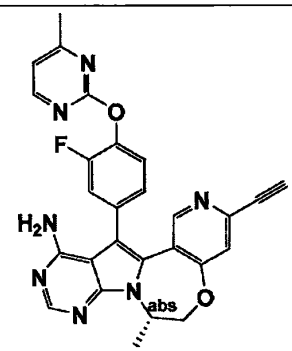
[2225] 3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺

[2226] 

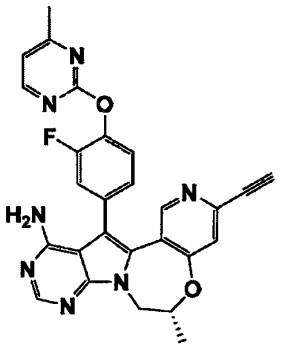
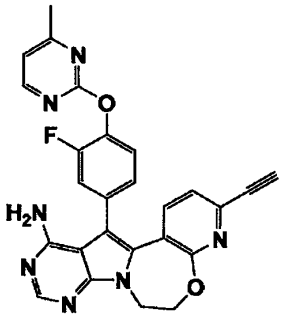
[2227] 步骤9:向圆底烧瓶中装入13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三异丙基硅烷基)乙炔基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(4.6g,7.23mmol)、四氢呋喃(60mL)及搅拌棒。添加TBAF(1.89g,7.23mmol),且在室温下搅拌溶液30分钟。所得粗物质通过硅胶色谱纯化(100g柱;用二氯甲烷/甲醇洗脱;比率=20:1)。真空浓缩,且然后用水(50mL)及ACN(100ml)洗涤残余物,产生呈浅黄色无定形固体状的3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5′,4′:4,5]吡咯并[1,2-d][1,4]氧氮杂环庚三烯-12-胺(3.00g,86%)。

[2228] 表50.示例性化合物

[2229]

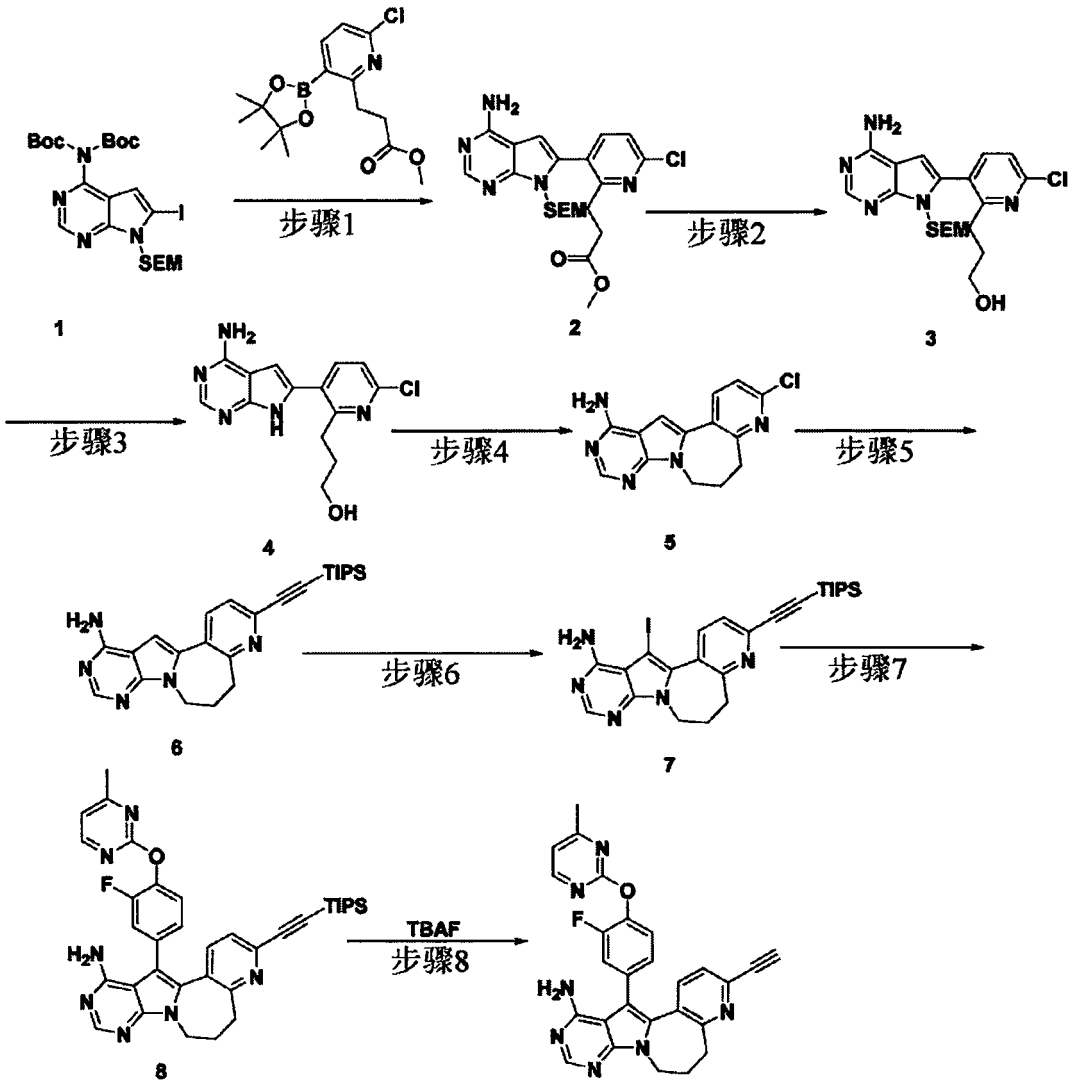
化合物	结构	质子 NMR	MS [M+1]
3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢吡啶并[3,4-f]嘧啶并[5',4':4,5]吡咯并[1,2-d][1,4]恶氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 8.02 (s, 1H), 7.54 - 7.41 (m, 2H), 7.34 - 7.27 (m, 1H), 7.25 (s, 1H), 7.22 (d, J = 5.1 Hz, 1H), 6.11 (s, 1H), 4.67 (s, 4H), 4.39 (s, 1H), 2.46 (s, 3H).	480.15
(R)-3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-6,7-二氢吡啶并[3,4-f]嘧啶并[5',4':4,5]吡咯并[1,2-d][1,4]恶氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) 8.54 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 8.05 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.36 (s, 1H), 7.29 - 7.17 (m, 2H), 5.76 (s, 1H), 5.62 -5.37 (m, 1H), 4.73 (dd, J = 12.8, 4.3 Hz, 1H), 4.60 (d, J = 12.6 Hz, 1H), 4.37 (s, 1H), 2.46 (s, 3H), 1.39 (d, J = 7.1 Hz, 3H).	494.20
(S)-3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-甲基-6,7-二氢吡啶并[3,4-f]嘧啶并[5',4':4,5]吡咯并[1,2-d][1,4]恶氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) 8.53 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.51-7.41 (m, 2H), 7.30-7.20 (m, 3H), 5.76 (s, 1H), 4.94 (td, J = 6.4, 2.8 Hz, 1H), 4.64 (dd, J = 15.3, 2.8 Hz, 1H), 4.42 (s, 1H), 4.34 (dd, J = 15.3, 6.4 Hz, 1H), 2.46 (s, 3H), 1.32 (d, J = 6.4 Hz, 3H).	494.20
(S)-3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-7-甲基-6,7-二氢吡啶并[3,4-f]嘧啶并[5',4':4,5]吡咯并[1,2-d][1,4]恶氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 8.05 (s, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 28.4 Hz, 1H), 7.23 - 7.16 (m, 2H), 6.12 (s, 1H), 5.54 - 5.39 (m, 1H), 4.73 (dd, J = 12.8, 4.3 Hz, 1H), 4.60 (d, J = 12.6 Hz, 1H), 4.37 (s, 1H), 2.46 (s, 3H), 1.39 (d, J = 7.2 Hz, 3H).	494.15

[2230]

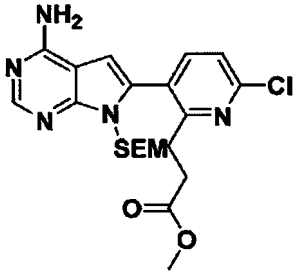
化合物	结构	质子 NMR	MS [M+1]
(R)-3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6-甲基-6,7-二氢吡啶并[3,4-f]嘧啶并[5',4':4,5]吡咯并[1,2-d][1,4]恶氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 8.04 (s, 1H), 7.57 - 7.35 (m, 2H), 7.34 - 7.17 (m, 3H), 6.21 (s, 1H), 4.94 (td, J = 6.4, 2.8 Hz, 1H), 4.65 (dd, J = 15.3, 2.9 Hz, 1H), 4.42 (s, 1H), 4.34 (dd, J = 15.3, 6.4 Hz, 1H), 2.46 (s, 3H), 1.32 (d, J = 6.4 Hz, 3H).	494.20
3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢吡啶并[3,2-f]嘧啶并[5',4':4,5]吡咯并[1,2-d][1,4]恶氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.49 - 7.34 (m, 3H), 7.29 - 7.20 (m, 3H), 6.15 (s, 1H), 4.64 (t, J = 5.1 Hz, 2H), 4.55 (t, J = 5.2 Hz, 2H), 4.44 (s, 1H), 2.45 (s, 3H).	480.20

[2231] 实例52

[2232] 流程49

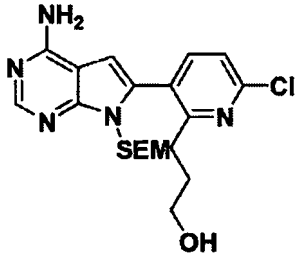
[2233] 

[2234] 3-(3-(4-氨基-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-6-氯吡啶-2-基)丙酸甲酯

[2235] 

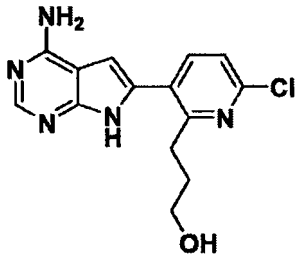
[2236] 步骤1:向圆底烧瓶中装入6-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺(23.8g,61.0mmol)、3-[6-氯-3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-2-基]丙酸甲酯(21.8g,67.1mmol)、Pd(dtbpf)Cl_2(3.97g,6.10mmol)、CsF(27.8g,183mmol)及搅拌棒。添加二恶烷/H_2O(500mL),且在90℃下搅拌溶液2小时。反应混合物用水(500mL)稀释,且水相用二氯甲烷(800mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(MeCN/H_2O=0%~50%;30分钟)。真空浓缩,产生呈黄色无定形固体状的3-[3-(4-氨基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-6-氯吡啶-2-基]丙酸甲酯(13g,46%)。

[2237] 3-(3-(4-氨基-7-((2-(三甲基硅烷基)乙氧基)甲基)-7H-吡咯并[2,3-d]嘧啶-6-基)-6-氯吡啶-2-基)丙-1-醇

[2238] 

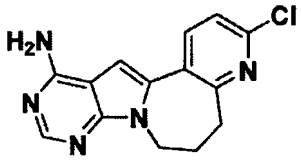
[2239] 步骤2:向圆底烧瓶中装入3-[3-(4-氨基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-6-氯吡啶-2-基]丙酸甲酯(13.0g,28.1mmol),添加四氢呋喃(200mL)。在-30℃下添加$LiAlH_4$(1.28g,33.7mmol)且在-30℃下搅拌溶液2小时。反应混合物用水(2.44mL)淬灭,且反应混合物经由硅藻土垫过滤,用DCM洗涤垫,且真空浓缩滤液。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇40:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的3-[3-(4-氨基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-6-氯吡啶-2-基]丙-1-醇(6.30g,52%)。

[2240] 3-(3-(4-氨基-7H-吡咯并[2,3-d]嘧啶-6-基)-6-氯吡啶-2-基)丙-1-醇

[2241] 

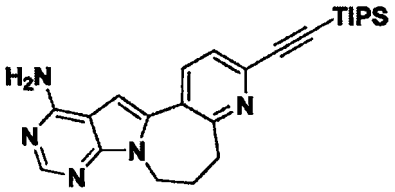
[2242] 步骤3:向圆底烧瓶中装入3-[3-(4-氨基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)-6-氯吡啶-2-基]丙-1-醇(5.00g,11.5mmol)及搅拌棒。添加HCl/MeOH(50mL),且在40℃下搅拌溶液1小时。真空浓缩反应混合物。然后用MeCN(20mL)稀释,反应混合物经由硅藻土垫过滤,用MeCN洗涤垫,及滤饼,产生呈灰白色无定形固体状的3-(3-{4-氨基-7H-吡咯并[2,3-d]嘧啶-6-基}-6-氯吡啶-2-基)丙-1-醇(3.00g,90%)。

[2243] 3-氯-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2244] 

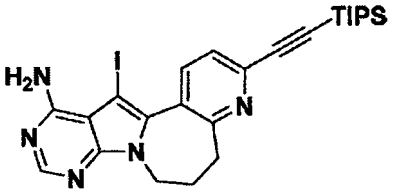
[2245] 步骤4:向可再密封的反应瓶中装入3-(3-{4-氨基-7H-吡咯并[2,3-d]嘧啶-6-基}-6-氯吡啶-2-基)丙-1-醇(3.50g,11.5mmol)、四氢呋喃(40mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DIAD(3.47g,17.2mmol)及PPh_3(4.52g,17.2mmol),且在25℃下搅拌混合物2小时。反应混合物用水(40mL)稀释,且水相用二氯甲烷(40mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇30:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的3-氯-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(2.00g,61%)。

[2246] 3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2247] 

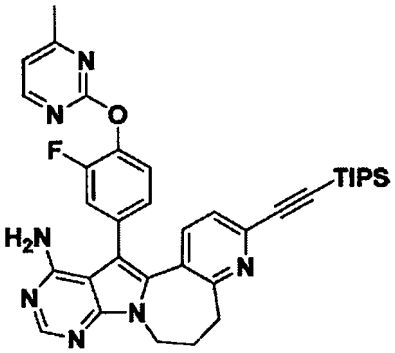
[2248] 步骤5:向可再密封的反应瓶中装入3-氯-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(1.98g,6.92mmol)、二甲基甲酰胺(20mL)、CuI(524mg,2.76mmol)、TEA(2.09g,20.7mmol)、Pd(dppf)Cl_2(505mg,692μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加乙炔基参(丙-2-基)硅烷(2.51g,13.8mmol),且在90℃下搅拌混合物2小时。反应混合物用水(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇40:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(1.50g,50%)。

[2249] 13-碘-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2250] 

[2251] 步骤6:向圆底烧瓶中装入3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(1.88g,4.35mmol)、二甲基甲酰胺(2mL)、NIS(978mg,4.35mmol)及搅拌棒,且在25℃下搅拌溶液1小时。反应混合物用Na_2SO_3(水溶液)(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇40:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的13-碘-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(1.50g,62%)。

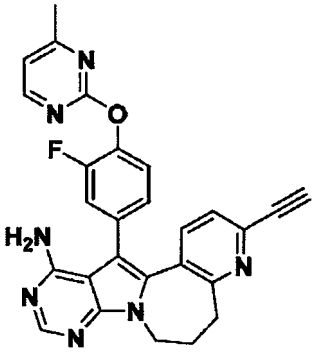
[2252] 13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2253] 

[2254] 步骤7:向可再密封的反应瓶中装入13-碘-3-((三异丙基硅烷基)乙炔基)-6,7-二

氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(1.48g,2.65mmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(960mg,2.91mmol)、K_3PO_4(1.68g,7.95mmol)、Pd(dppf)Cl_2(193mg,265μmol),添加DME/H_2O(20mL),及搅拌棒,随后抽真空且用氮气吹扫三次,且在90℃下搅拌混合物1小时。反应混合物用水(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱(用二氯甲烷/甲醇30:1洗脱)纯化。真空浓缩,产生呈黄色无定形固体状的13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(1g,60%)。

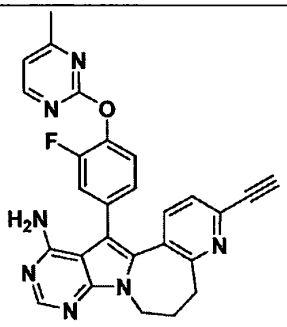
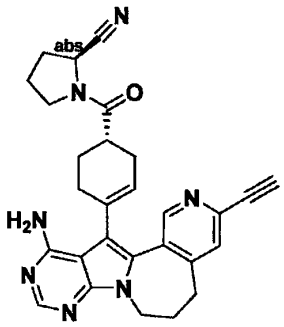
[2255] 3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2256] 

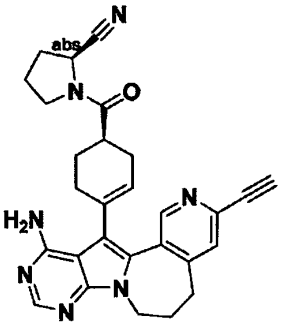
[2257] 步骤8:向圆底烧瓶中装入13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(980mg,1.55mmol)、四氢呋喃(20mL)、TBAF(2.07mL,2.07mmol)及搅拌棒,且在25℃下搅拌溶液1小时。反应混合物用水(20mL)稀释,且水相用二氯甲烷(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过HPLC纯化(柱:YMC-Actus Triart C18,30*250,5um;移动相A:水(10MMOL/L NH_4HCO_3),移动相B:ACN;流量:60mL/min;梯度:25B至60B,历时7分钟;254/220nm;RT1:6.32)。冻干产生呈灰白色无定形固体状的3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(250mg,34%)。

[2258] 表51.示例性化合物

[2259]

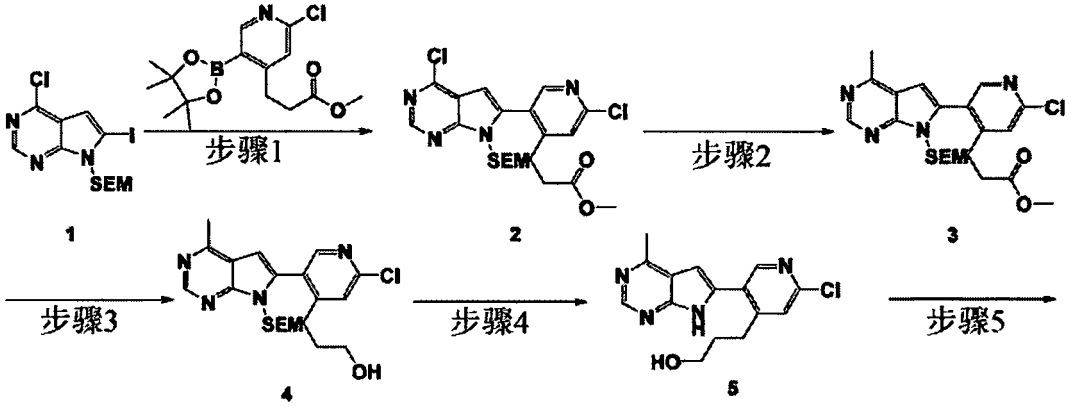
化合物	结构	质子 NMR	MS [M+1]
3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,2-c]嘧啶并[5',4':4,5]吡咯并[1,2-a]氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 7.45 - 7.35 (m, 3H), 7.29 - 7.19 (m, 3H), 6.12 (s, 2H), 4.41 (s, 1H), 4.17 (d, J = 7.0 Hz, 2H), 2.92 (t, J = 7.1 Hz, 2H), 2.44 (s, 3H), 2.31 (q, J = 6.8 Hz, 2H).	478.20
(S)-1-((S)-4-(12-氨基-3-乙炔基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5',4':4,5]吡咯并[1,2-a]氮呼-13-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.15 (s, 1H), 7.66 (s, 1H), 6.80 (s, 1H), 5.89 (s, 1H), 4.74 (dd, J = 7.4, 3.4 Hz, 1H), 4.43 (s, 1H), 4.09 (s, 2H), 3.77 (s, 1H), 3.53 (q, J = 8.4 Hz, 1H), 3.02 - 2.89 (m, 1H), 2.66 (d, J = 7.0 Hz, 2H), 2.34 (d, J = 6.1 Hz, 2H), 2.29 - 1.93 (m, 8H), 1.80 - 1.74 (m, 2H).	478.25

[2260]

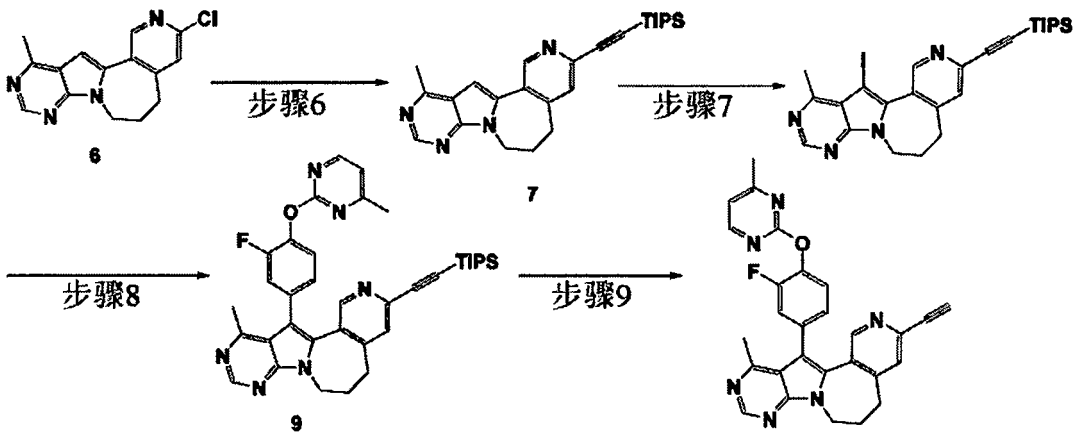
化合物	结构	质子 NMR	MS [M+1]
(S)-1-((R)-4-(12-氨基-3-乙炔基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5',4':4,5]吡咯并[1,2-a]氮呼-13-基)环己-3-烯-1-羰基)吡咯烷-2-甲腈		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.11 (s, 1H), 7.65 (s, 1H), 6.61 (d, J = 46.1 Hz, 1H), 5.87 (s, 1H), 4.75 (dd, J = 7.9, 3.7 Hz, 1H), 4.42 (s, 1H), 4.20 (s, 1H), 3.96 (s, 1H), 3.83 - 3.47 (m, 2H), 2.98 (d, J = 5.9 Hz, 1H), 2.76 - 2.59 (m, 2H), 2.33 (s, 2H), 2.28 - 2.10 (m, 4H), 2.04 (d, J = 6.7 Hz, 4H), 1.80 (d, J = 6.2 Hz, 2H).	478.25

[2261] 实例53

[2262] 流程50

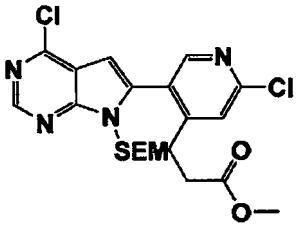


[2263]



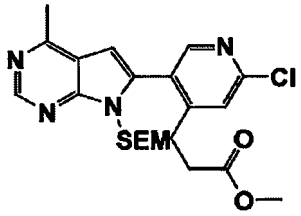
[2264] 3-[2-氯-5-(4-氯-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙酸甲酯

[2265]



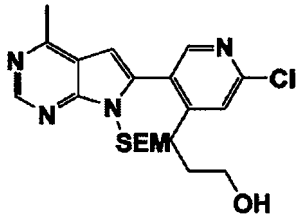
[2266] 步骤1:向可再密封的反应瓶中装入4-氯-6-碘-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(5g,12.2mmol)、{2-[6-氯-4-(3-甲氧基-3-侧氧基丙基)吡啶-3-基]-4,5,5-三甲基-1,3,2-二氧杂硼杂环戊烷-4-基}甲基鎓(4.73g,14.6mmol)、CsF(5.54g,36.5mmol)、Pd(dtbpf)Cl_2(795mg,1.22mmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二恶烷/H_2O(100mL),且在70℃下搅拌混合物1小时。反应混合物用H_2O(400mL)稀释,且水相用二氯甲烷(200mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(300g柱;用PE/EA 30/1洗脱)。真空浓缩,产生呈黑色无定形固体状的3-[2-氯-5-(4-氯-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙酸甲酯(2.00g,34.0%)。

[2267] 3-[2-氯-5-(4-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙酸甲酯

[2268] 

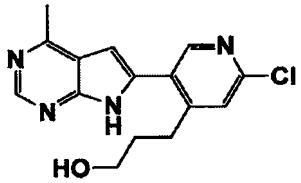
[2269] 步骤2:向可再密封的反应瓶中装入3-[2-氯-5-(4-氯-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙酸甲酯(1.9g,3.94mmol)、Pd(PPh_3)$_4$(455mg,394μmol)、二甲基甲酰胺(25mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二甲基锌(413mg,4.33mmol),且在90℃下搅拌混合物2小时。反应混合物用H_2O(100mL)稀释,且水相用EA(80mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(300g柱;用PE/EA 10/1洗脱)。真空浓缩,产生呈黑色无定形固体状的3-[2-氯-5-(4-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙酸甲酯(850mg,46.9%)。

[2270] 3-[2-氯-5-(4-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙-1-醇

[2271] 

[2272] 步骤3:向圆底烧瓶中装入3-[2-氯-5-(4-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙酸甲酯(800mg,1.73mmol)、四氢呋喃(10mL)及搅拌棒。添加铝氧烷氢化锂(98.2mg,2.59mmol),且在-30℃下搅拌溶液。反应混合物用H_2O(50mL)淬灭,且水相用二氯甲烷(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩,产生呈灰白色无定形固体状的3-[2-氯-5-(4-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙-1-醇(570mg,76.1%)。

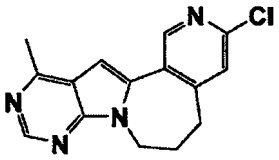
[2273] 3-(2-氯-5-{4-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡啶-4-基)丙-1-醇

[2274] 

[2275] 步骤4:向圆底烧瓶中装入3-[2-氯-5-(4-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-6-基)吡啶-4-基]丙-1-醇(550mg,1.27mmol)及搅拌棒。添加MeOH/HCl(10mL),且在40℃下搅拌溶液1小时。真空浓缩溶液。然后添加MeOH(5mL),添加乙二胺(76.3mg,1.27mmol),且在室温下搅拌溶液30分钟。反应混合物用H_2O(50mL)稀释,且水相用DCM(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩,产生呈灰白色无定形固体状的3-(2-氯-5-{4-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡啶-4-基)丙-1-醇(360mg,93.7%)。

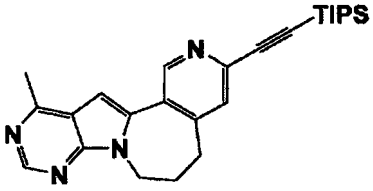
[2276] 3-氯-12-甲基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]

氮呼

[2277] 

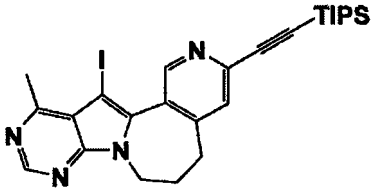
[2278] 步骤5:向可再密封的反应瓶中装入3-(2-氯-5-{4-甲基-7H-吡咯并[2,3-d]嘧啶-6-基}吡啶-4-基)丙-1-醇(340mg,1.12mmol)、PPh_3(510mg,1.68mmol)、四氢呋喃(10mL)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DIAD(655mg,1.68mmol),且在40℃下搅拌混合物1小时。反应混合物用H_2O(50mL)稀释,且水相用二氯甲烷(50mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。残余物通过硅胶色谱纯化(300g柱;用PE/EA 1/1洗脱)。真空浓缩,产生呈灰白色无定形固体状的3-氯-12-甲基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼(180mg,56.6%)。

[2279] 12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼

[2280] 

[2281] 步骤6:向可再密封的反应瓶中装入3-氯-12-甲基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼(160mg,561μmol)、TEA(169mg,1.68mmol)、CuI(42.5mg,224μmol)、Pd(pddf)Cl_2(81.9mg,112μmol)、三(丙-2-基)硅烷(88.8mg,561μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加二甲基甲酰胺(10mL),且在70℃下搅拌混合物2小时。反应混合物用H_2O(50mL)稀释,且水相用EA(20mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用已烷/乙酸乙酯15/1洗脱)。真空浓缩,产生呈橙色无定形固体状的12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼(150mg,62.2%)。

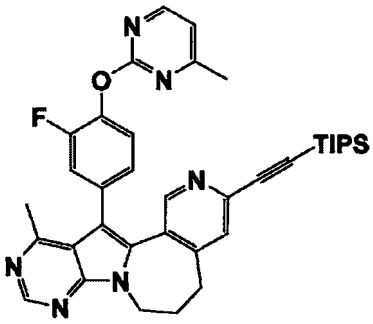
[2282] 13-碘-12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼

[2283] 

[2284] 步骤7:向圆底烧瓶中装入12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼(150mg,348μmol)、二氯甲烷(5mL)、TFA(118mg,1.04mmol)及搅拌棒。在0℃下添加1-碘吡咯烷-2,5-二酮(85.9mg,382μmol),且在室温下搅拌溶液30分钟。混合物用饱和$NaHSO_3$水溶液淬灭直至pH至8-9,用DCM(100mL*3)萃取,合并有机相且经Na_2SO_4干燥,真空浓缩,产生13-碘-12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼(180mg,

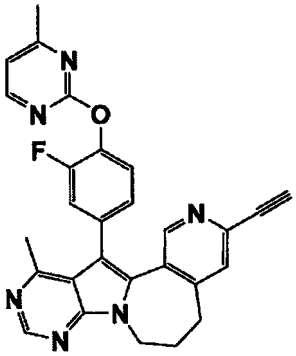
93.2%)。

[2285] 13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呯

[2286] 

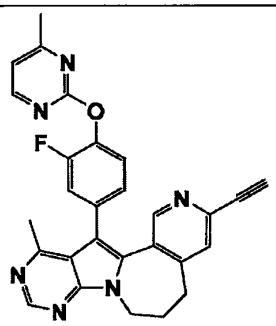
[2287] 步骤8:向可再密封的反应瓶中装入13-碘-12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呯(160mg,287μmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(113mg,344μmol)、K_3PO_4(182mg,861μmol)、$Pd(PPh_3)_4$(331mg,287μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME/H_2O(6mL),且在90℃下搅拌混合物1小时。反应混合物用H_2O(50mL)稀释,且水相用二氯甲烷(30mL)萃取三次。合并的有机层用盐水洗涤,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过硅胶色谱纯化(50g柱;用己烷/乙酸乙酯1/1洗脱)。真空浓缩,产生呈黑色无定形固体状的13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呯(100mg,55.2%)。

[2288] 3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-12-甲基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呯

[2289] 

[2290] 步骤9:向圆底烧瓶中装入13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-12-甲基-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呯(90mg,142μmol)、四氢呋喃(1mL)及搅拌棒。添加TBAF(34.4mg,142μmol),且在室温下搅拌溶液。反应混合物用DCM(100mL)稀释,合并的有机层用H_2O(200ml)洗涤六次,经硫酸钠干燥,过滤且真空浓缩。所得粗物质通过制备型HPLC纯化(柱:YMC-Actus Triart C18,20*250MM,5um,12nm;移动相A:未定义;移动相B:未定义;流量:60mL/min;梯度:40B至65B,历时8分钟;220/254nm;RT1:7.07)。冻干产生呈灰白色无定形固体状的3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-12-甲基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呯(18.9mg,27.9%)。

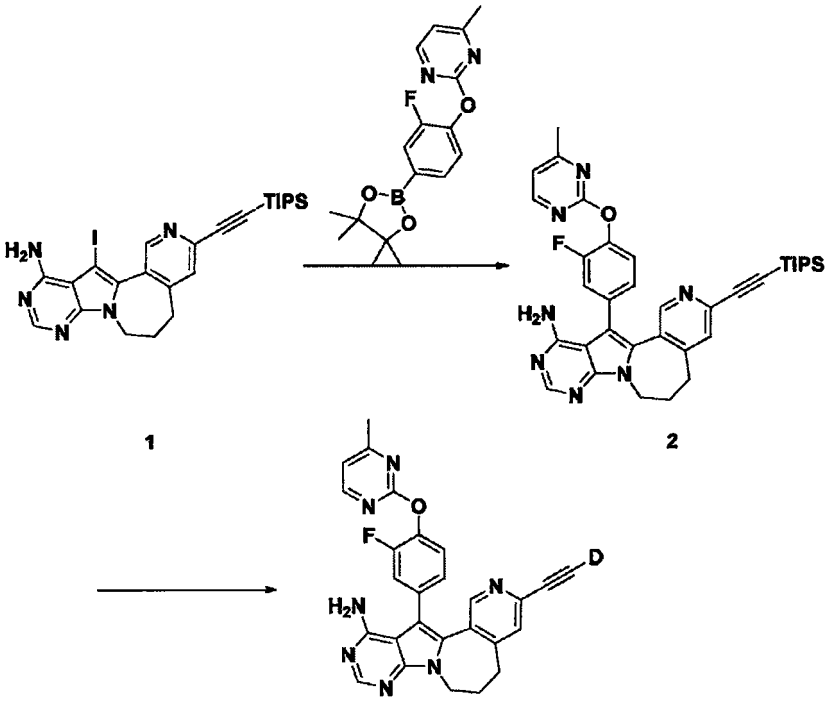
[2291] 表52.示例性化合物

化合物	结构	质子 NMR	MS [M+1]
3-乙炔基-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-12-甲基-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5',4':4,5]吡咯并[1,2-a]氮呼		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.51 (d, J = 5.1 Hz, 1H), 8.12 (s, 1H), 7.71 (s, 1H), 7.50 (d, J = 11.2 Hz, 1H), 7.42 (t, J = 8.3 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 5.0 Hz, 1H), 4.44 (s, 1H), 4.27 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 7.0 Hz, 2H), 2.43 (d, J = 9.3 Hz, 6H), 2.29 (t, J = 6.9 Hz, 2H).	477.25

[2292]

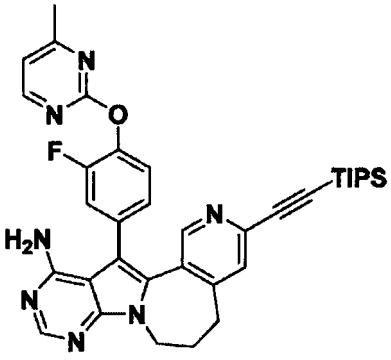
[2293] 实例54

[2294] 流程51

[2295] 

1 2

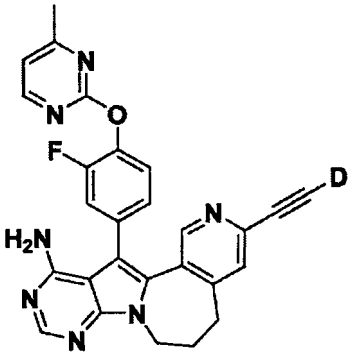
[2296] 13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2297] 

[2298] 向可再密封的反应瓶中装入13-碘-3-((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(180mg,322μmol)、2-[2-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基]-4-甲基嘧啶(159mg,482μ

mol)、K_3PO_4(204mg,965μmol)、Pd(PPh_3)$_4$(37.1mg,32.1μmol)及搅拌棒,随后抽真空且用氮气吹扫三次。添加DME:H_2O=10:1(3mL),且在90℃下搅拌溶液2小时。反应混合物用水淬灭,用DCM萃取,经Na_2SO_4干燥,真空浓缩。所得粗物质通过制备型TLC纯化(DCM:MeOH=15:1)。真空浓缩,产生呈黄色无定形固体状的13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(90.0mg,44%)。

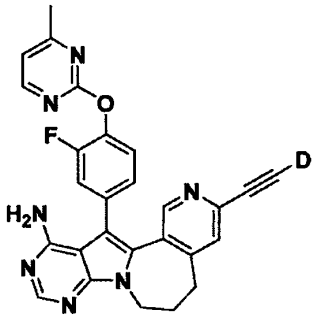
[2299] 3-(乙炔基-d)-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺

[2300] 

[2301] 向可再密封的反应瓶中装入13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-3((三异丙基硅烷基)乙炔基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(90mg,141μmol)、TBAF(14.7mg,56.4μmol)、D_2O(310mg,15.5mmol)、四氢呋喃(2mL)及搅拌棒。反应混合物在微波反应器中、在100℃下搅拌30分钟。冷却后,移除溶剂,残余物通过制备型TLC来纯化(DCM:MeOH=15:1)。然后自ACN中再结晶,产生呈灰白色无定形固体状的3-(乙炔基-d)-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5′,4′:4,5]吡咯并[1,2-a]氮呼-12-胺(11.8mg,17%)。

[2302] 表53.示例性化合物

[2303]

化合物	结构	质子 NMR	MS [M+1]
3-(乙炔基-d)-13-(3-氟-4-((4-甲基嘧啶-2-基)氧基)苯基)-6,7-二氢-5H-吡啶并[3,4-c]嘧啶并[5',4':4,5]吡咯并[1,2-a]氮呼-12-胺		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 5.0 Hz, 1H), 8.21 (s, 1H), 8.04 (s, 1H), 7.68 (s, 1H), 7.49 - 7.33 (m, 2H), 7.28 - 7.18 (m, 2H), 5.76 (s, 1H), 4.15 (t, J = 6.7 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.45 (s, 3H), 2.30-2.22 (m, 2H).	479.15

[2304] 实例55

[2305] 本发明的化合物还在FGFR2生物化学Caliper分析中加以测试。化合物在10mM DMSO溶液中制备且依据3倍稀释度连续稀释成11种浓度。向384孔板中添加200nL化合物溶液且添加15uL的1.3x酶溶液(FGFR2蛋白质(0.06nM)、FLPeptide30(1.5uM)、$MgCl_2$(10mM))且培养板在室温下培育30分钟。添加5uL ATP溶液(100uM)以起始反应且将培养板培育90分钟,然后添加70uL中止缓冲液(0.5M EDTA)以终止反应。使用EZ读取器分析各孔。

[2306] FGFR2生物化学Caliper分析结果呈现于表1中。IC50小于或等于100nM的化合物表

示为“A”;IC50大于100nM、但小于或等于250nM的化合物表示为“B”;IC50大于250nM、但小于或等于1μM的化合物表示为“C”;且IC50大于1μM、但小于或等于100μM的化合物表示为“D”。

[2307] 实例56

[2308] 本发明的化合物还在SNU16癌细胞系增殖分析中加以测试。测试化合物制备成10mM DMSO储备溶液。将45uL储备溶液转移至384孔板中,且进行3倍11点稀释。SNU16细胞接种于384孔细胞培养板中且在37度下培育24小时。利用Echo550液体操纵器从化合物板转移40nL各种浓度的化合物至细胞培养板的对应孔中。培养板培育96小时,然后相对于室温平衡15分钟。向各孔中添加20uL CellTiter Glo试剂,然后在室温下轻缓地振荡培养板30分钟。然后在EnVision读取器读取化学发光。

[2309] SNU16癌细胞系增殖分析结果呈现于表1中。IC50小于或等于100nM的化合物表示为“A”;IC50大于100nM、但小于或等于250nM的化合物表示为“B”;IC50大于250nM、但小于或等于1μM的化合物表示为“C”;且IC50大于1μM、但小于或等于100μM的化合物表示为“D”。

[2310] 以引用的方式并入

[2311] 本文提及的所有公开及专利以全文引用的方式并入本文中用于所有目的,如同各个别公开或专利特定地且个别地以引用的方式并入一般。在有冲突的情况下,以本申请(包括本文中的任何定义)为准。

[2312] 等效物

[2313] 虽然本公开的特定实施例已加以论述,但以上说明书具有说明性而非限制性。本领域中的技术人元在审阅本说明书后将显而易知本公开的许多变化形式。本公开的完整范畴以及其等效物的完整范畴,及说明书,以及此类变化形式,应参照申请专利范围确定。

[2314] 除非另外指明,否则说明书及申请专利范围中所使用的表示成分数量、反应条件等所有数字均应理解为在所有情况下由术语“约”修饰。因此,除非有相反指示,否则本说明书及所附申请专利范围中所阐述的数值参数是近似值,其可视本公开设法获得的所需特性而变化。