

氨基嘧啶类化合物及其制备方法和应用

技术领域

- 5 本发明涉及氨基嘧啶类化合物及其制备方法和应用，特别涉及抑制、调节和 / 或调控 EGFR 激酶的信号转导的化合物、它们的制备方法、含有它们的药物组合物以及它们的应用。

背景技术

- 10 蛋白激酶是信号传导途径的酶组分,它催化末端磷酸盐从 ATP 迁移至蛋白的酪氨酸、丝氨酸和 / 或苏氨酸残基的羟基。因此,抑制蛋白激酶功能的化合物是评估蛋白激酶活动的生理学结果的有价值的工具。哺乳动物的正常或突变蛋白激酶的过表达或不适当表达已经成为广泛研究的主题,并已经被证实在许多疾病,包括糖尿病、血管生成、银屑病、再狭窄、眼病、精神分裂症、类风湿性关节炎、动脉粥样硬化、心血管疾病和癌症
- 15 的发展中起到重要作用。蛋白激酶抑制剂在治疗人和动物疾病方面具有特别的用途。

- 实现细胞调节的主要机制之一是通过跨膜胞外信号转导来进行的,该转导转而调控细胞内的生化通路。蛋白质磷酸化代表了一种过程,通过该过程胞内信号在分子与分子间传播,最终导致细胞应答。蛋白质磷酸化主要发生在丝氨酸、苏氨酸或酪氨酸残基上,因此已经按照其磷酸化位点的特异性对蛋白激酶进行了分类,即丝氨酸 / 苏氨酸激酶和
- 20 酪氨酸激酶。由于磷酸化是细胞内的普遍过程并且由于细胞表型主要受这些通路活性的影响,所以目前认为许多疾病状态和 / 或疾病可归因于激酶级联分子成分的异常活化或功能突变。

- EGFR 是受体酪氨酸激酶 ErbB 受体家族成员。EGFR 的过度表达 (上调) 或过度活动已经与许多癌症相关,包括头颈部癌,卵巢癌,宫颈癌,膀胱癌,食道癌,胃癌,乳
- 25 腺癌,子宫内膜癌,结肠直肠癌,非小细胞肺癌,和胶质母细胞瘤。

- EGFR 作为一种致癌基因产生了针对 EGFR 小分子抑制剂的抗癌疗法。例如针对非小细胞肺癌 (NSCLC) 的吉非替尼 (易瑞沙) 和厄洛替尼 (特罗凯)。然而,许多患者治疗一段时间后就会产生耐药性,其中一个主要原因是 T790M 突变。T790M 增加了 EGFR 对 ATP 的亲合力,这是最常见的可逆酪氨酸激酶抑制剂的获得性耐药性的机制。不可逆
- 30 的 EGFR 抑制剂能够共价烷基化位于活性中心的半胱氨酸残基 (Cys797) 从而克服可逆

抑制剂的这种获得性耐药性。

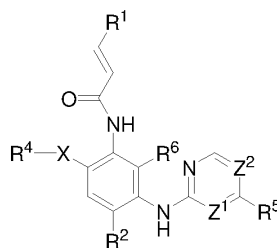
在 50%-80% 的 NSCLC 病人中，他们的 EGFR 都过度表达，从而引起癌变。已经应用于临床的第一代 EGFR 抑制剂如易瑞沙、特罗凯等，它们对于 NSCLC 的治疗取得了很大成功。但临床有非常明显的皮疹和腹泻等副作用，而且在使用一年后，患者对药物
5 出现耐药性。临床数据显示，大约有 50% 的患者获得性耐药源于 T790M 位点的突变。第二代抑制剂如阿法替尼，与 EGFR 的结合活性更强，但对 T790M 突变体的选择性差，药物无法在体内达到其有效浓度。

为了更好的解决第一代抑制剂的耐药问题及第二代抑制剂的选择性问题，开发选择性抑制 T790M 的第三代抑制剂具有重要意义。

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发明内容

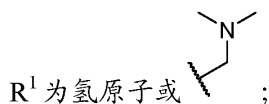
本发明提供了一种较高 EGFR T790M 选择抑制性的新型氨基嘧啶类化合物，具有如下式 I 所示的结构，



I

15

其中



R¹ 为氢原子或

R² 为 C₁₋₆ 烷基或 OR⁸，R⁸ 为氢原子，C₁₋₈ 烷基，卤代 C₁₋₈ 烷基，C₃₋₈ 环烷基，卤代 C₃₋₈ 环烷基，C₃₋₇ 环烷基-C₁₋₆ 烷基，取代或未取代含有 1-2 个选自 N、O 和 S 中的杂原子的 4-7 元杂环基，取代或未取代含有 1-2 个选自 N、O 和 S 中的杂原子的 4-7 元杂环基-C₁₋₈ 烷基；

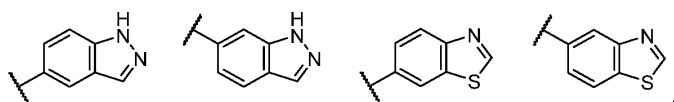
X 为化学键、O、S、CO、NR³ 或 CR³，其中 R³ 为氢，C₁₋₆ 烷基，卤代 C₁₋₆ 烷基，C₃₋₈ 环烷基，卤代 C₃₋₈ 环烷基，C₁₋₆ 烷氧基-C₁₋₆ 烷基，C₁₋₈ 烷基-CO 或 4-6 元杂环基；

R⁴ 为 C₁₋₆ 烷基，C₃₋₆ 环烷基，4-7 元杂环基或 4-7 元双环桥杂环基，它们可以任选
25 地被 1-3 个独立地选自下组的取代基所取代：C₁₋₆ 烷基，卤代 C₁₋₆ 烷基，C₁₋₆ 烷氧基，卤代 C₁₋₆ 烷氧基，C₃₋₆ 环烷基，卤代 C₃₋₆ 环烷基，C₃₋₆ 环烷氧基，卤代 C₃₋₆ 环烷氧基，

C₁₋₆ 烷氧基-C₁₋₆ 烷基, 羟基-C₁₋₆ 烷基, 氨基-C₁₋₆ 烷基, C₁₋₆ 烷基-氨基-C₁₋₆ 烷基, 卤素, 羟基, 氰基, 氰基-C₁₋₈ 烷基, 氨基, C₁₋₆ 烷基-氨基, 二(C₁₋₆ 烷基)-氨基, C₃₋₆ 环烷基-氨基, C₁₋₆ 烷基羰基, C₁₋₆ 烷基-氨基-酰基, 二(C₁₋₆ 烷基)-氨基-酰基, C₃₋₆ 环烷基-氨基-酰基, C₁₋₆ 酰基-氨基, 取代或未取代的杂环基, 取代或未取代的杂环基-烷基, 其中所

5 述取代基可选择地和它们所连接的碳原子一起形成环;

R⁵ 为由两个环形成的并环, 选自



所述的并环非必需地由 1-3 个取代基所取代, 所述的取代基为 C₁₋₆ 烷基, 卤代 C₁₋₆ 烷基, C₁₋₆ 烷氧基, 卤代 C₁₋₆ 烷氧基, C₃₋₆ 环烷基, 卤代 C₃₋₆ 环烷基, C₃₋₆ 环烷氧基, 卤
10 代 C₃₋₆ 环烷氧基, C₁₋₆ 烷氧基-C₁₋₆ 烷基, 羟基-C₁₋₆ 烷基, 氨基-C₁₋₆ 烷基, C₁₋₆ 烷基-氨基-C₁₋₆ 烷基, 卤素, 羟基, 氰基, 氰基-C₁₋₈ 烷基, 氨基, C₁₋₆ 烷基-氨基, 二(C₁₋₆ 烷基)-氨基, C₃₋₆ 环烷基-氨基, C₁₋₆ 烷基-氨基-酰基, 二(C₁₋₆ 烷基)-氨基-酰基, C₃₋₆ 环烷基-氨基-酰基, C₁₋₆ 酰基-氨基, 取代或未取代的杂环基, 取代或未取代的杂环基-烷基, 其中所述取代基可选择地和它们所连接的碳原子一起形成环;

15 R⁶ 为氢, 卤素, 羟基, 腈基, C₁₋₃ 烷基, 卤代 C₁₋₃ 烷基, C₃₋₆ 环烷基, 卤代 C₃₋₆ 环烷基, C₁₋₃ 烷氧基, 卤代 C₁₋₃ 烷氧基, C₃₋₆ 环烷氧基, 卤代 C₃₋₆ 环烷氧基;

Z¹ 为 C-R⁷, Z² 为 N, 或者 Z¹ 为 N, Z² 为 C-R⁷ (即其中 Z¹ 和 Z² 不同时为 N), 其中 R⁷ 为氢, 卤素, 腈基, C₁₋₃ 烷基, 卤代 C₁₋₃ 烷基, C₃₋₆ 环烷基, 卤代 C₃₋₆ 环烷基。

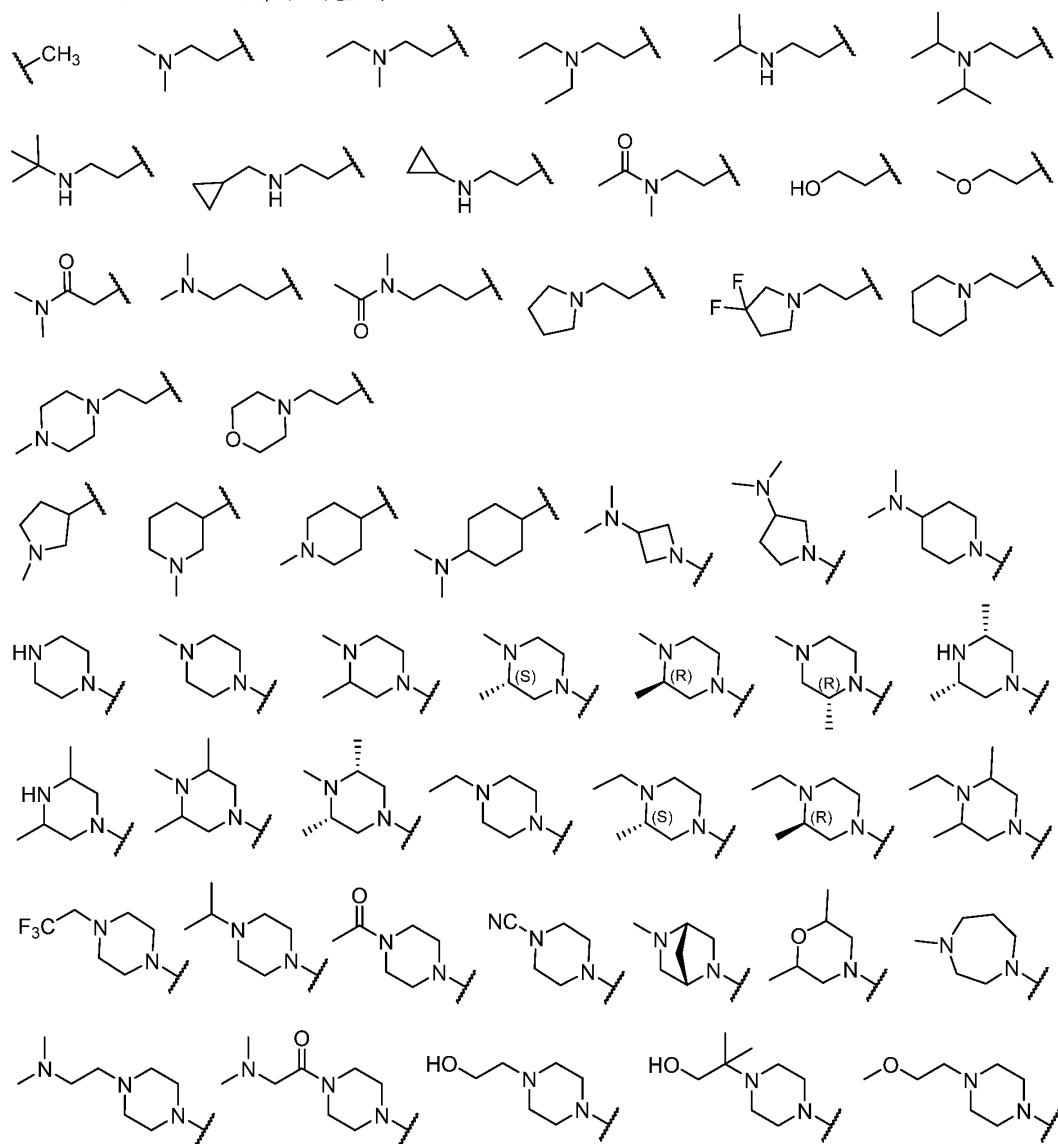
在某些实施方式中, R² 为 OR⁸, R⁸ 为 C₁₋₅ 烷基, 卤代 C₁₋₅ 烷基, C₃₋₇ 环烷基, 卤代
20 C₃₋₇ 环烷基或 C₃₋₇ 环烷基-甲基; 优选地, R² 为 OR⁸, R⁸ 为甲基, 乙基, 正丙基, 异丙基, 环丙基, 二氟甲基, 三氟甲基, 环丁基, 或环丙基甲基;

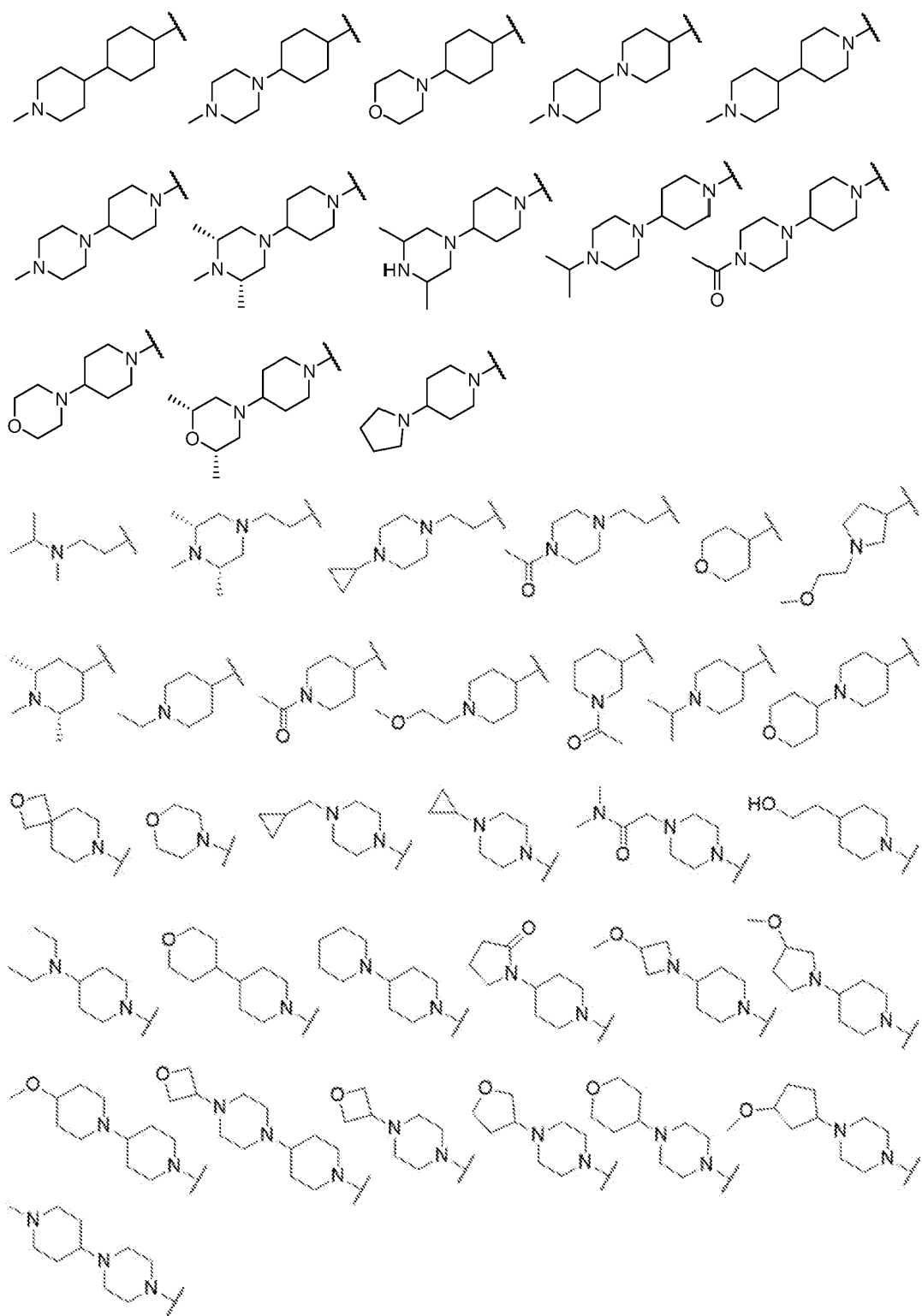
在某些实施方式中, X 为化学键或 NR³, 其中 R³ 为氢, 甲基, 乙基, 甲氧基乙基;

在某些实施方式中, R⁴ 为 C₁₋₃ 烷基, C₃₋₆ 环烷基, 包含 1-2 个选自 N、O 和 S 的杂
25 原子的 4-7 元杂环基或 4-7 元双环桥杂环基, 它们可以任选地被 1-3 个独立地选自下组的取代基所取代: C₁₋₆ 烷基, 卤代 C₁₋₆ 烷基, C₁₋₆ 烷氧基, 卤代 C₁₋₆ 烷氧基, C₃₋₆ 环烷基, 卤代 C₃₋₆ 环烷基, C₃₋₆ 环烷氧基, 卤代 C₃₋₆ 环烷氧基, C₁₋₆ 烷氧基-C₁₋₆ 烷基, 羟基-C₁₋₆ 烷基, 氨基-C₁₋₆ 烷基, C₁₋₆ 烷基-氨基-C₁₋₆ 烷基, 卤素, 羟基, 氰基, 氰基-C₁₋₈ 烷基, 氨基, C₁₋₆ 烷基-氨基, 二(C₁₋₆ 烷基)-氨基, C₃₋₆ 环烷基-氨基, C₁₋₆ 烷基羰基,

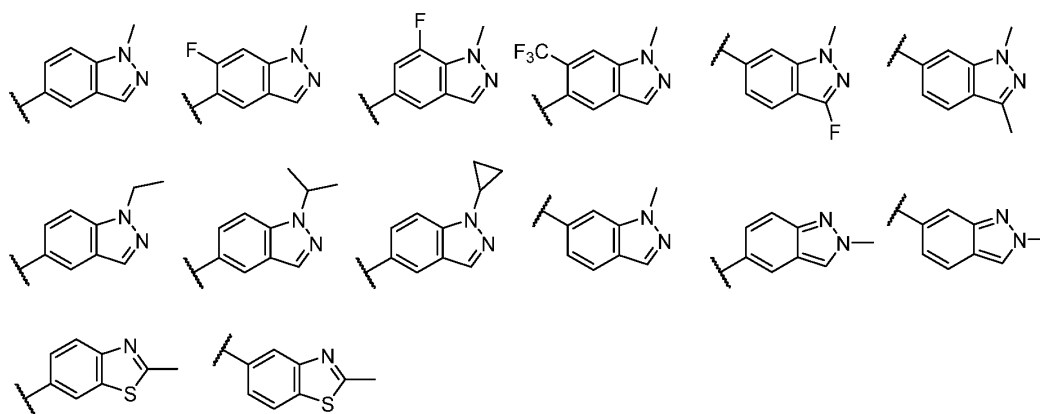
C₁₋₆ 烷基-氨基-酰基, 二(C₁₋₆ 烷基)-氨基-酰基, C₃₋₆ 环烷基-氨基-酰基, C₁₋₆ 酰基-氨基, 取代或未取代的 4-7 元杂环基;

优选地, R⁴ 选自下列基团:





5 在某些实施方式中，R⁵选自下列基团：



在某些实施方式中， R^6 为氢，卤素，羟基，腈基， C_{1-3} 烷基，卤代 C_{1-3} 烷基， C_{1-3} 烷氧基，卤代 C_{1-3} 烷氧基。

- 5 在某些实施方式中， Z^1 为 $C-R^7$ ， Z^2 为 N，或者 Z^1 为 N， Z^2 为 $C-R^7$ ，其中 R^7 为氢。

在某些具体实施方案中，在式 I 中：

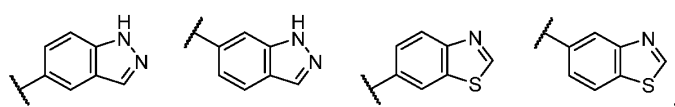
R^1 为氢原子；

- 10 R^2 为 OR^8 ， R^8 为 C_{1-5} 烷基，卤代 C_{1-5} 烷基， C_{3-7} 环烷基，卤代 C_{3-7} 环烷基或 C_{3-7} 环烷基-甲基；

X 为化学键或 NR^3 ，其中 R^3 为氢， C_{1-6} 烷基（例如甲基，乙基）、甲氧基乙基；

- 15 R^4 为 C_{1-3} 烷基， C_{3-6} 环烷基，包含 1-2 个选自 N、O 和 S 的杂原子的 4-7 元杂环基或 4-7 元双环桥杂环基，它们可以任选地被 1-3 个独立地选自下组的取代基所取代： C_{1-6} 烷基，卤代 C_{1-6} 烷基， C_{1-6} 烷氧基，卤代 C_{1-6} 烷氧基， C_{3-6} 环烷基，卤代 C_{3-6} 环烷基， C_{3-6} 环烷氧基，卤代 C_{3-6} 环烷氧基， C_{1-6} 烷氧基- C_{1-6} 烷基，羟基- C_{1-6} 烷基，氨基- C_{1-6} 烷基， C_{1-6} 烷基-氨基- C_{1-6} 烷基，卤素，羟基，氰基，氰基- C_{1-8} 烷基，氨基， C_{1-6} 烷基-氨基，二（ C_{1-6} 烷基）-氨基， C_{3-6} 环烷基-氨基， C_{1-6} 烷基羰基， C_{1-6} 烷基-氨基-酰基，二（ C_{1-6} 烷基）-氨基-酰基， C_{3-6} 环烷基-氨基-酰基， C_{1-6} 酰基-氨基，取代或未取代的 4-7 元杂环基；

- 20 R^5 为由两个环形成的并环，选自



所述的并环非必需地由 1-3 个取代基所取代，所述的取代基为 C_{1-6} 烷基，卤代 C_{1-6} 烷基， C_{1-6} 烷氧基，卤代 C_{1-6} 烷氧基， C_{3-6} 环烷基，卤代 C_{3-6} 环烷基， C_{3-6} 环烷氧基，卤

代 C₃₋₆ 环烷基, C₁₋₆ 烷氧基-C₁₋₆ 烷基, 羟基-C₁₋₆ 烷基, 氨基-C₁₋₆ 烷基, C₁₋₆ 烷基-氨基-C₁₋₆ 烷基, 卤素, 羟基, 氰基, 氰基-C₁₋₈ 烷基, 氨基, C₁₋₆ 烷基-氨基, 二(C₁₋₆ 烷基)-氨基, C₃₋₆ 环烷基-氨基, C₁₋₆ 烷基-氨基-酰基, 二(C₁₋₆ 烷基)-氨基-酰基, C₃₋₆ 环烷基-氨基-酰基, C₁₋₆ 酰基-氨基, 取代或未取代的杂环基, 取代或未取代的杂环基-烷基, 其中

5 所述取代基可选择地和它们所连接的碳原子一起形成环;

R⁶ 为氢, 卤素, 羟基, 腈基, C₁₋₃ 烷基, 卤代 C₁₋₃ 烷基, C₁₋₃ 烷氧基, 卤代 C₁₋₃ 烷氧基;

Z^1 为 $C-R^7$, Z^2 为 N , 或者 Z^1 为 N , Z^2 为 $C-R^7$, 其中 R^7 为氢。

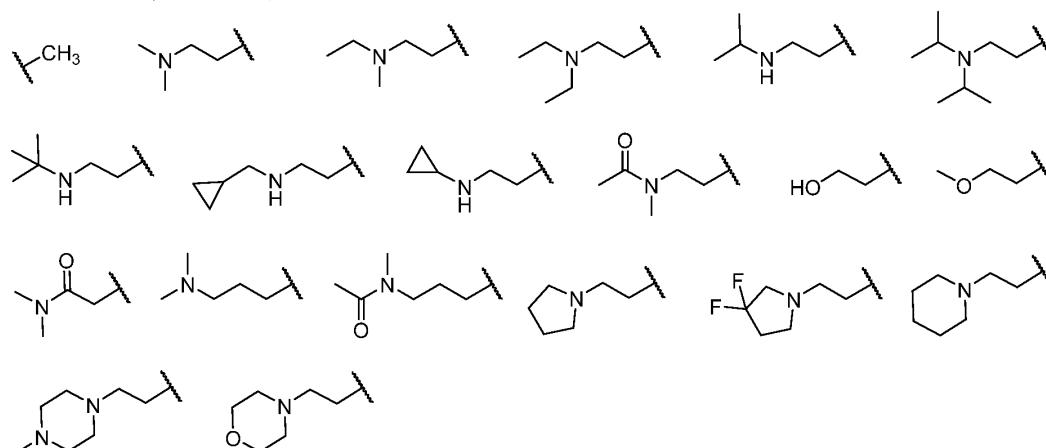
在另一些具体实施方案中，在式 I 中：

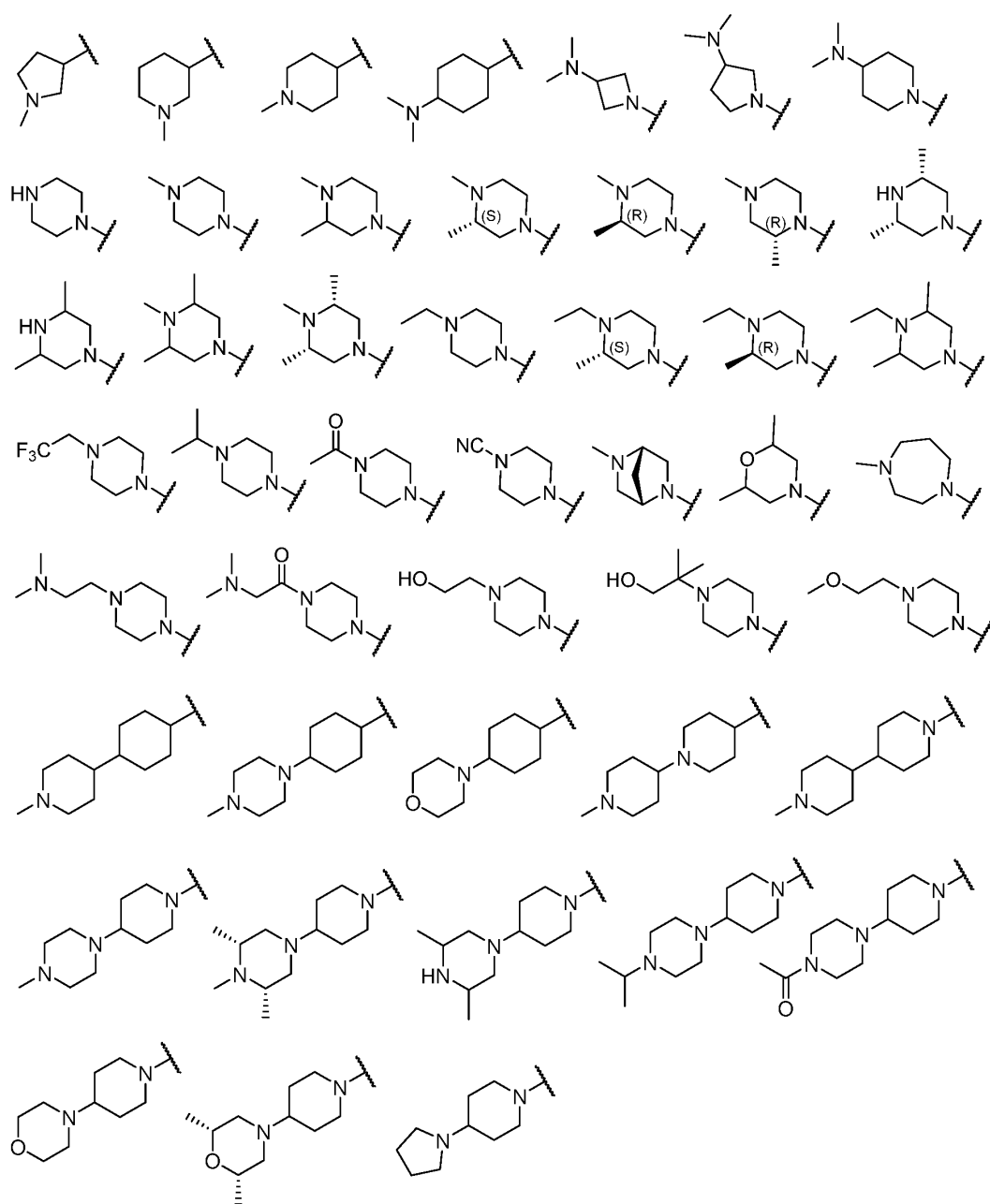
10 R^1 为氢原子;

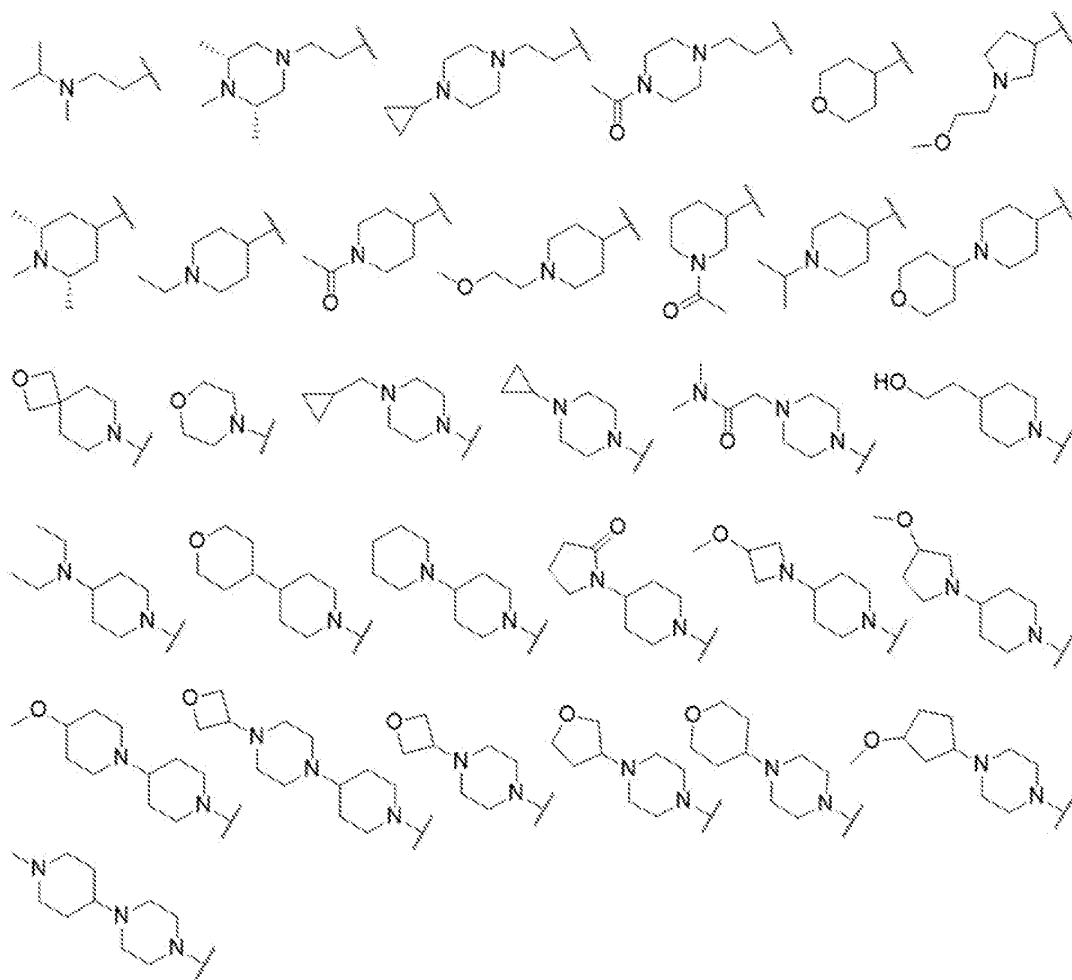
R^2 为 OR^8 , R^8 为甲基, 乙基, 正丙基, 异丙基, 环丙基, 二氟甲基, 三氟甲基, 环丙基甲基;

X为化学键或NR³，其中R³为氢，C₁₋₆烷基（例如甲基，乙基）、甲氧基乙基；

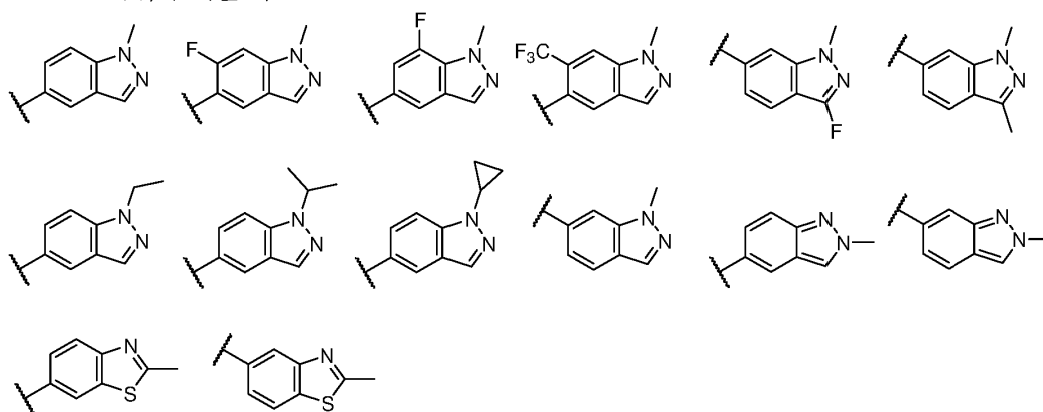
R⁴选自下列基团:







R^5 选自下列基团:



5

R^6 为氢, 卤素;

Z^1 为 $C-R^7$, Z^2 为 N, 或者 Z^1 为 N, Z^2 为 $C-R^7$, 其中 R^7 为氢。

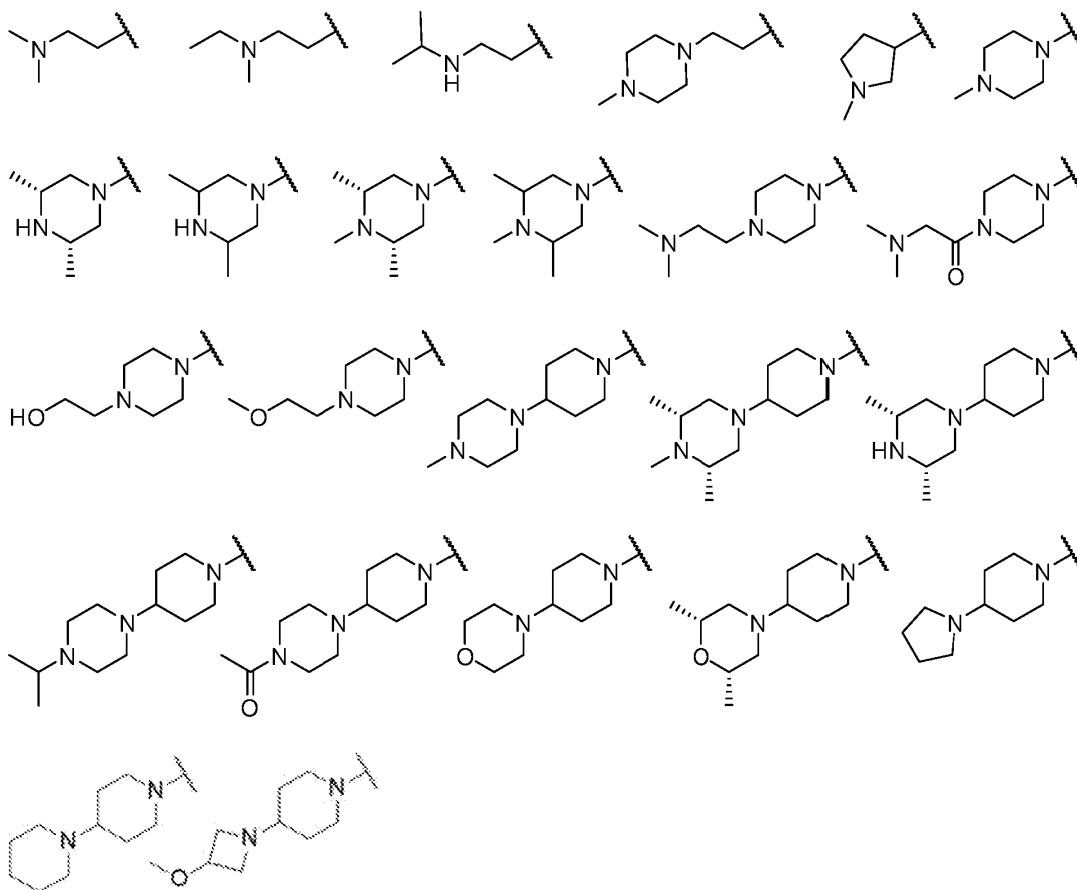
在又一些具体实施方案中，在式 I 中：

R^1 为氢原子；

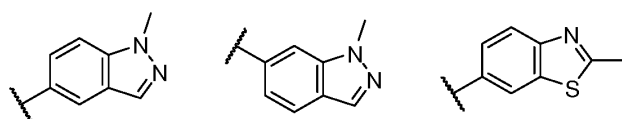
R^2 为 OR^8 ， R^8 为甲基，乙基，二氟甲基；

5 X 为化学键或 NR^3 ，其中 R^3 为氢， C_{1-6} 烷基（例如甲基，乙基）；

R^4 选自下列基团：



R^5 选自下列基团：



R^6 为氢或卤素；

Z^1 为 $C-R^7$ ， Z^2 为 N，或者 Z^1 为 N， Z^2 为 $C-R^7$ ，其中 R^7 为氢。

在某些实施方式中，本申请提供了包含上述化合物以及药学上可接受的载体或赋形

剂的药物组合物。在某些实施方式中，药物组合物为片剂、胶囊剂、丸剂、颗粒剂、散剂、栓剂、注射剂、溶液剂、混悬剂、膏剂、贴剂、洗剂、滴剂、擦剂、喷雾剂。

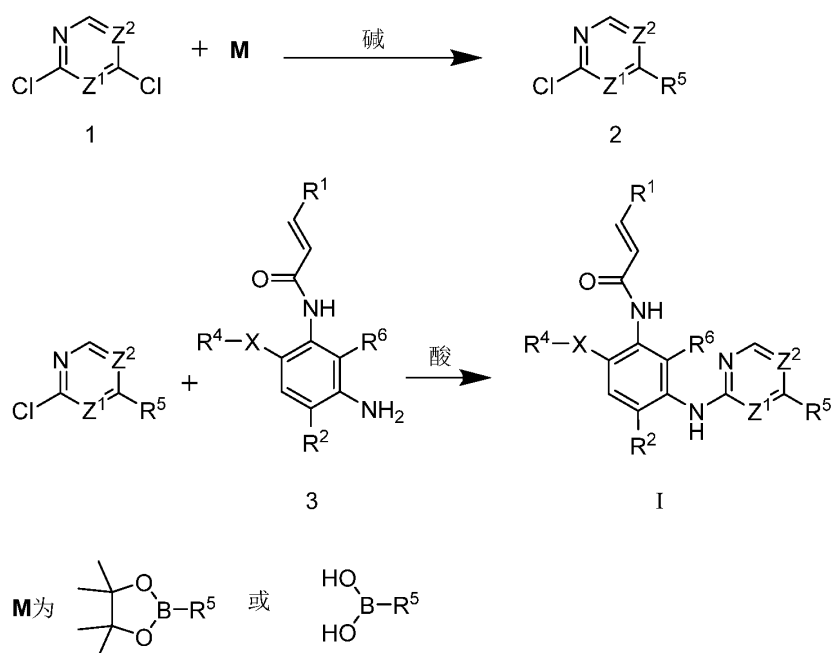
在某些实施方式中，本申请提供了包含上述化合物和/或药物组合物在制备抗肿瘤药物中的应用。在某些实施方式中，所述抗肿瘤药物应用于以下病症：头颈部癌，黑色素
5 瘤，膀胱癌，食道癌，间变性大细胞淋巴瘤，肾细胞癌，乳腺癌，结肠直肠癌，卵巢癌，宫颈癌，胰腺癌，胶质瘤，胶质母细胞瘤，前列腺癌，白血病，淋巴瘤，非霍奇金淋巴瘤，胃癌，肺癌，肝细胞癌，胃肠道基质瘤，甲状腺癌，胆管癌，子宫内膜癌，多发性骨髓瘤或间皮瘤。

在某些实施方式中，本申请提供了治疗主体中肿瘤的方法，包括向所述主体给予有
10 效量的上述化合物或药物组合物，所述的主体优选哺乳动物，所述哺乳动物优选为人。

在某些实施方式中，给药方式包括口腔、粘膜、舌下、眼部、局部、肠道外、直肠、脑池、阴道、腹膜、膀胱、鼻部给药。

在某些实施方式中，所述肿瘤包括：头颈部癌，黑色素瘤，膀胱癌，食道癌，间变性大细胞淋巴瘤，肾细胞癌，乳腺癌，结肠直肠癌，卵巢癌，宫颈癌，胰腺癌，胶质瘤，
15 胶质母细胞瘤，前列腺癌，白血病，淋巴瘤，非霍奇金淋巴瘤，胃癌，肺癌，肝细胞癌，胃肠道基质瘤，甲状腺癌，胆管癌，子宫内膜癌，多发性骨髓瘤或间皮瘤。

在某些实施方式中，本申请提供了一种制备式 I 化合物的方法，包括使化合物 1 与化合物 M 在碱性条件下反应，形成化合物 2，然后再使化合物 2 与化合物 3 在酸性条件下反应形成式 I 化合物的步骤；



其中 R^1 、 R^2 、 R^4 、 R^5 、 R^6 、 X 、 Z^1 和 Z^2 如前述所定义，

优选地，所述碱为碳酸钠或碳酸氢钠；

5 优选地，所述酸为甲磺酸或对甲苯磺酸；

在某些实施方式中，所述制备式 I 化合物的方法包括如下反应步骤：

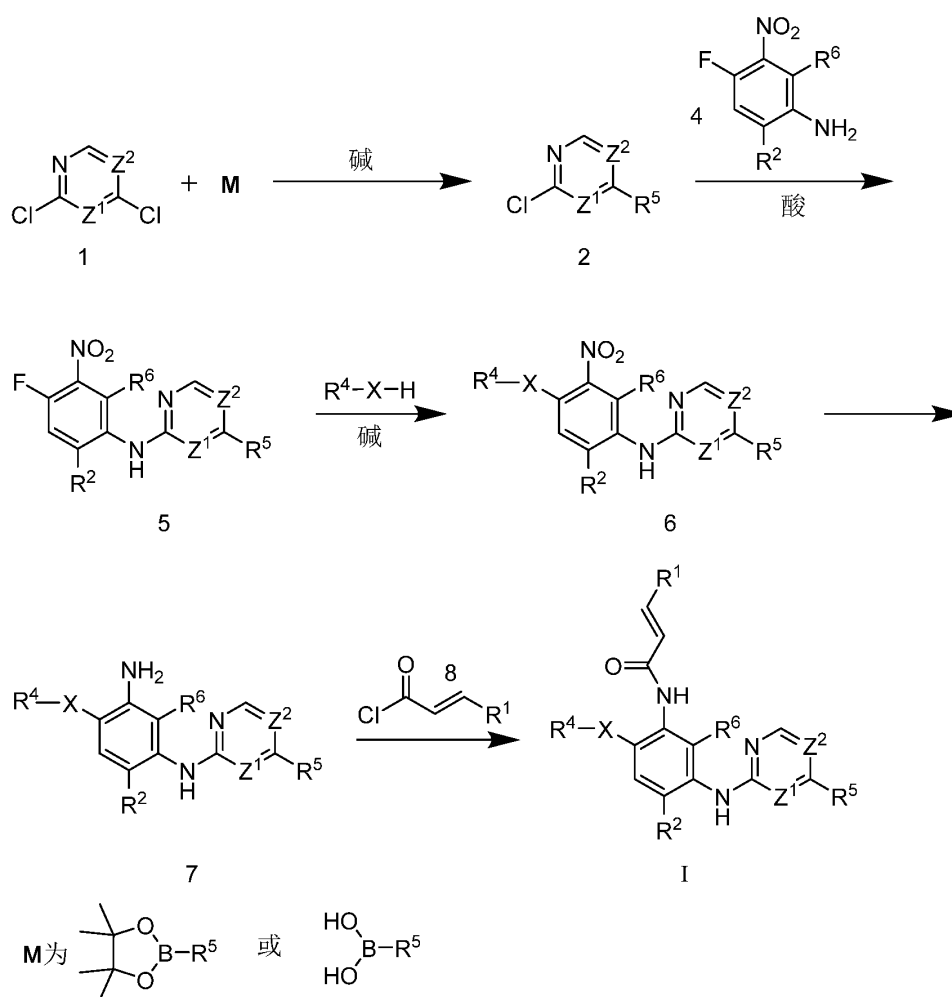
(1) 使化合物 1 与化合物 M 在碱性条件下反应，形成化合物 2；

(2) 使化合物 2 与化合物 4 在酸性条件下反应形成化合物 5；

(3) 使化合物 5 与 $\text{R}^4\text{-X-H}$ 在碱性条件下反应形成化合物 6；

10 (4) 将化合物 6 还原为化合物 7；

(5) 使化合物 7 与化合物 8 反应，形成式 I 所示的化合物；



其中 R^1 、 R^2 、 R^4 、 R^5 、 R^6 、X、 Z^1 和 Z^2 如前述所定义。

优选地，在步骤（1）中，所述碱为碳酸钠或碳酸氢钠；

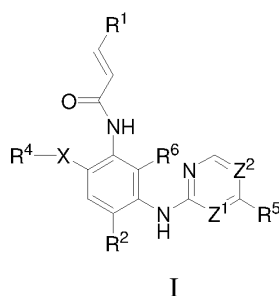
5 优选地，在步骤（2）中，所述酸为甲磺酸或对甲苯磺酸；

优选地，在步骤（3）中，所述碱选自二异丙基乙胺，碳酸钠和三乙胺。

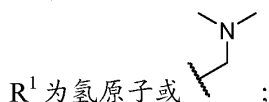
本发明的其它特点和优势可见下面的详细叙述。以下实施例和具体实施方式旨在清楚说明本发明的技术方案及其技术效果和优势，并非限制本发明的范围。

作为 EGFR 激酶抑制剂的化合物的结构

10 本发明涉及式 I 化合物或者其药学上可接受的盐、立体异构体、前药分子或溶剂合物



其中

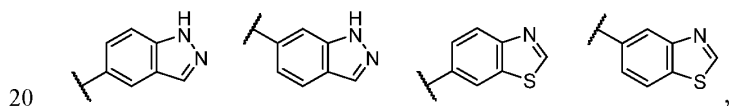


- 5 R^2 为 C_{1-6} 烷基或 OR^8 , R^8 为氢原子, C_{1-8} 烷基, 卤代 C_{1-8} 烷基, C_{3-8} 环烷基, 卤代 C_{3-8} 环烷基, C_{3-7} 环烷基- C_{1-6} 烷基, 取代或未取代含有 1-2 个选自 N、O 和 S 中的杂原子的 4-7 元杂环基, 取代或未取代含有 1-2 个选自 N、O 和 S 中的杂原子的 4-7 元杂环基- C_{1-8} 烷基;

- X 为化学键、O、S、CO、 NR^3 或 CR^3 , 其中 R^3 为氢, C_{1-6} 烷基, 卤代 C_{1-6} 烷基, C_{3-8} 环烷基, 卤代 C_{3-8} 环烷基, C_{1-6} 烷氧基- C_{1-6} 烷基, C_{1-8} 烷基-CO 或 4-6 元杂环基;

- R^4 为 C_{1-6} 烷基, C_{3-6} 环烷基, 4-7 元杂环基或 4-7 元双环桥杂环基, 它们可以任选地被 1-3 个独立地选自下组的取代基所取代: C_{1-6} 烷基, 卤代 C_{1-6} 烷基, C_{1-6} 烷氧基, 卤代 C_{1-6} 烷氧基, C_{3-6} 环烷基, 卤代 C_{3-6} 环烷基, C_{3-6} 环烷氧基, 卤代 C_{3-6} 环烷氧基, C_{1-6} 烷氧基- C_{1-6} 烷基, 羟基- C_{1-6} 烷基, 氨基- C_{1-6} 烷基, C_{1-6} 烷基-氨基- C_{1-6} 烷基, 卤素, 羟基, 氰基, 氰基- C_{1-8} 烷基, 氨基, C_{1-6} 烷基-氨基, 二(C_{1-6} 烷基)-氨基, C_{3-6} 环烷基-氨基, C_{1-6} 烷基羰基, C_{1-6} 烷基-氨基-酰基, 二(C_{1-6} 烷基)-氨基-酰基, C_{3-6} 环烷基-氨基-酰基, C_{1-6} 酰基-氨基, 取代或未取代的杂环基, 取代或未取代的杂环基-烷基, 其中所述取代基可选择地和它们所连接的碳原子一起形成环;

R^5 为由两个环形成的并环, 选自



所述的并环非必需地由 1-3 个取代基所取代, 所述的取代基为 C_{1-6} 烷基, 卤代 C_{1-6} 烷基, C_{1-6} 烷氧基, 卤代 C_{1-6} 烷氧基, C_{3-6} 环烷基, 卤代 C_{3-6} 环烷基, C_{3-6} 环烷氧基, 卤代 C_{3-6} 环烷氧基, C_{1-6} 烷氧基- C_{1-6} 烷基, 羟基- C_{1-6} 烷基, 氨基- C_{1-6} 烷基, C_{1-6} 烷基-氨基- C_{1-6} 烷基, 卤素, 羟基, 氰基, 氰基- C_{1-8} 烷基, 氨基, C_{1-6} 烷基-氨基, 二(C_{1-6} 烷基)

-氨基, C₃₋₆ 环烷基-氨基, C₁₋₆ 烷基-氨基-酰基, 二 (C₁₋₆ 烷基)-氨基-酰基, C₃₋₆ 环烷基-氨基-酰基, C₁₋₆ 酰基-氨基, 取代或未取代的杂环基, 取代或未取代的杂环基-烷基, 其中所述取代基可选择地和它们所连接的碳原子一起形成环:

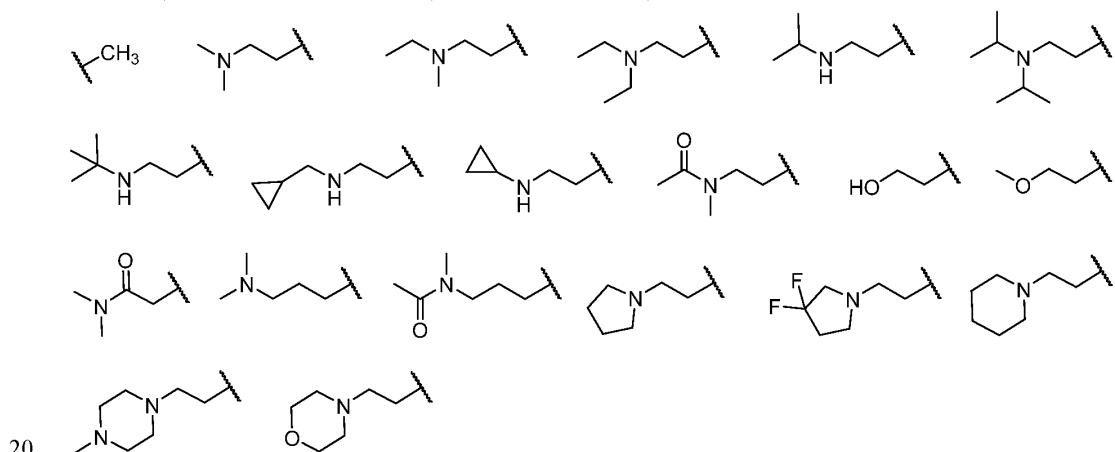
5 R^6 为氢, 卤素, 羟基, 腈基, C_{1-3} 烷基, 卤代 C_{1-3} 烷基, C_{3-6} 环烷基, 卤代 C_{3-6} 环烷基, C_{1-3} 烷氧基, 卤代 C_{1-3} 烷氧基, C_{3-6} 环烷氧基, 卤代 C_{3-6} 环烷氧基;

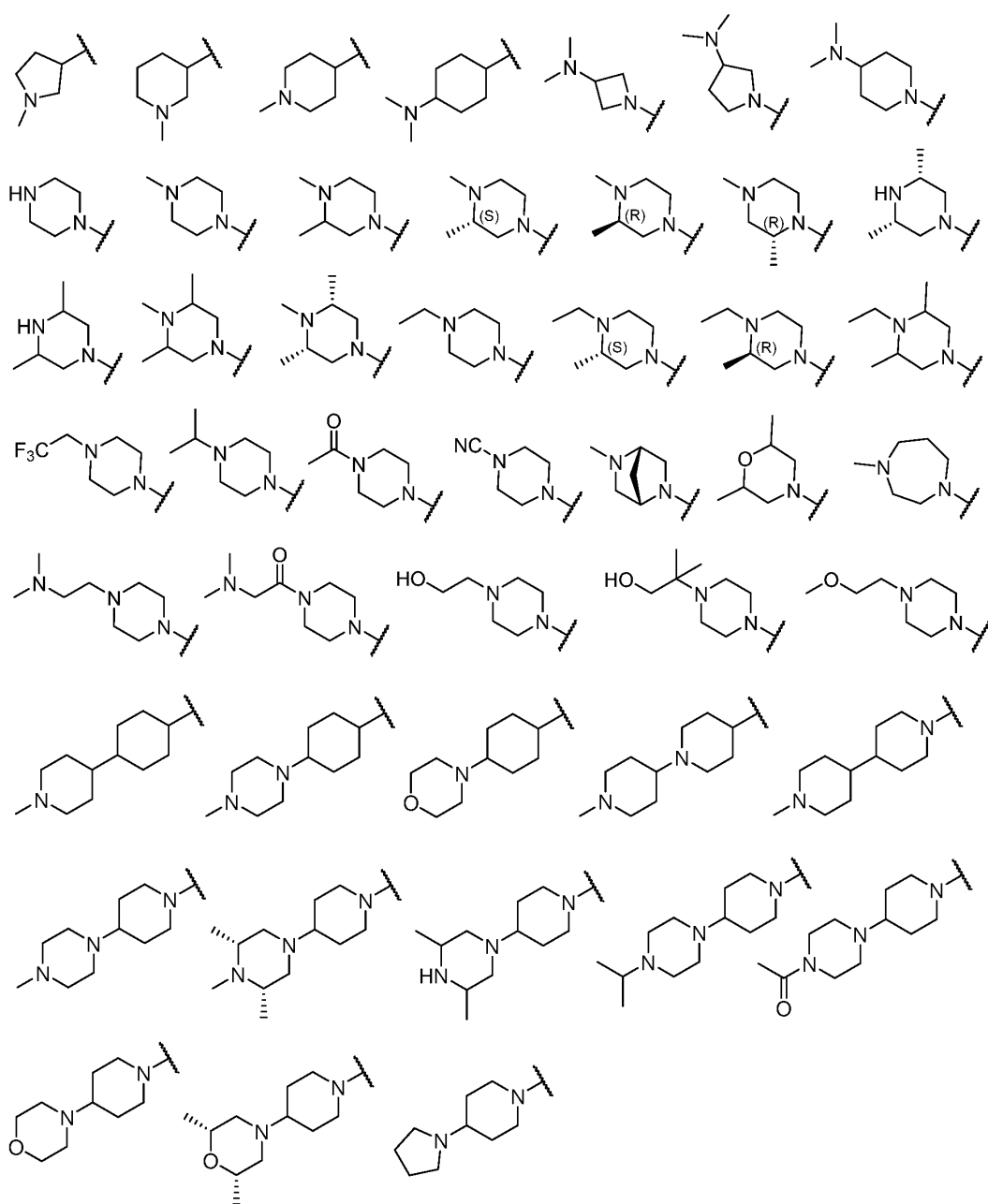
Z^1 为 C-R⁷, Z^2 为 N, 或者 Z^1 为 N, Z^2 为 C-R⁷ (即其中 Z^1 和 Z^2 不同时为 N), 其中 R⁷ 为氢, 卤素, 腈基, C₁₋₃ 烷基, 卤代 C₁₋₃ 烷基, C₃₋₆ 环烷基, 卤代 C₃₋₆ 环烷基。

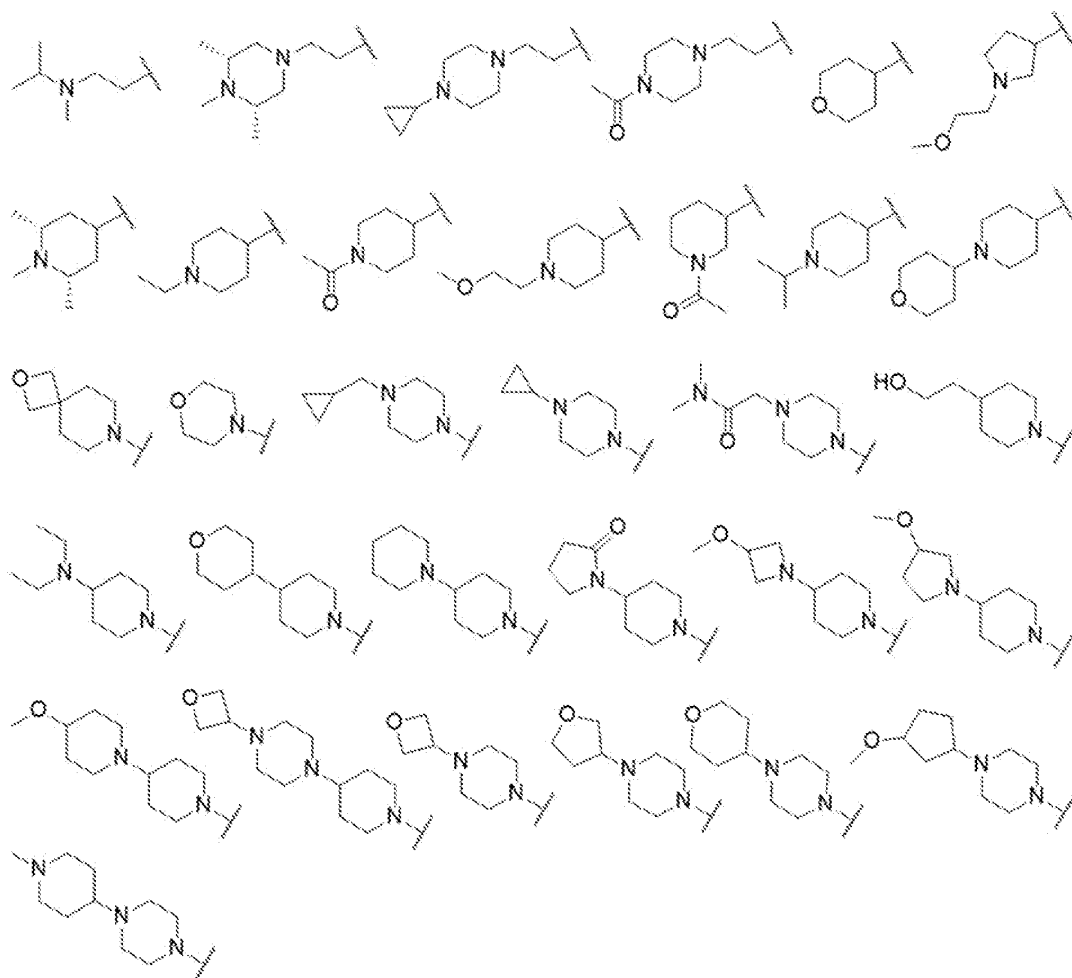
在某些实施方式中，R²为OR⁸，R⁸为C₁₋₅烷基，卤代C₁₋₅烷基，C₃₋₇环烷基，卤代C₃₋₇环烷基或C₃₋₇环烷基-甲基；优选地，R²为OR⁸，R⁸为甲基，乙基，正丙基，异丙基，环丙基，二氟甲基，三氟甲基，环丁基，或环丙基甲基。

在某些实施方式中，X为化学键或NR³，其中R³为氢，甲基，乙基，甲氧基乙基。

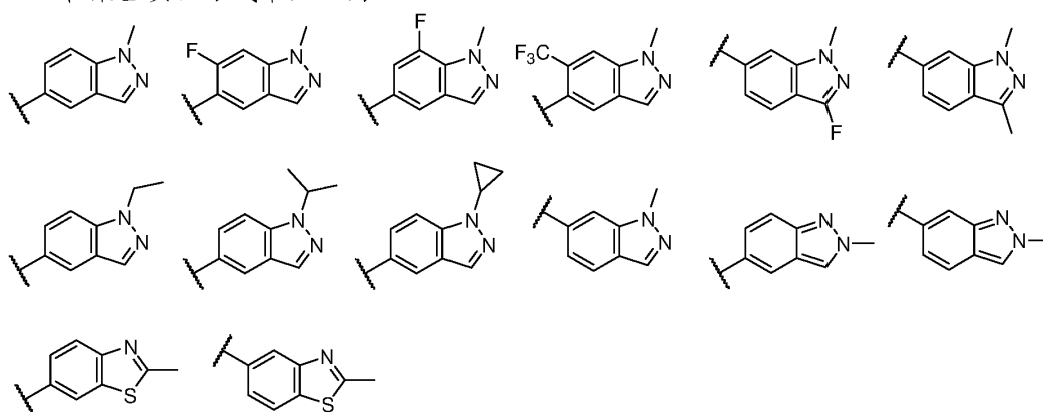
在某些实施方式中， R^4 为 C_{1-3} 烷基， C_{3-6} 环烷基，包含 1-2 个选自 N、O 和 S 的杂原子的 4-7 元杂环基或 4-7 元双环桥杂环基，它们可以任选地被 1-3 个独立地选自下组的取代基所取代： C_{1-6} 烷基，卤代 C_{1-6} 烷基， C_{1-6} 烷氧基，卤代 C_{1-6} 烷氧基， C_{3-6} 环烷基，卤代 C_{3-6} 环烷基， C_{3-6} 环烷氧基，卤代 C_{3-6} 环烷氧基， C_{1-6} 烷氧基- C_{1-6} 烷基，羟基- C_{1-6} 烷基，氨基- C_{1-6} 烷基， C_{1-6} 烷基-氨基- C_{1-6} 烷基，卤素，羟基，氰基，氰基- C_{1-8} 烷基，氨基， C_{1-6} 烷基-氨基，二(C_{1-6} 烷基)-氨基， C_{3-6} 环烷基-氨基， C_{1-6} 烷基羰基， C_{1-6} 烷基-氨基-酰基，二(C_{1-6} 烷基)-氨基-酰基， C_{3-6} 环烷基-氨基-酰基， C_{1-6} 酰基-氨基，取代或未取代的 4-7 元杂环基；优选地， R^4 选自下列基团：







在某些实施方式中， R^5 为



在某些实施方式中 R^6 为氢，卤素，羟基，腈基， C_{1-3} 烷基，卤代 C_{1-3} 烷基， C_{1-3} 烷氧基，卤代 C_{1-3} 烷氧基。

在某些实施方式中 Z^1 为 $C-R^7$ ， Z^2 为 N，或者 Z^1 为 N， Z^2 为 $C-R^7$ ，其中 R^7 为氢。

除非另外指出，阐明下列定义以举例说明和定义用于描述本发明的各种术语的含义

和范围。

碳氢基团中碳原子含量的最小值和最大值通过前缀表示，例如，前缀(C_{a-b})烷基表示任何含“a”至“b”个碳原子的烷基。因此，例如，(C₁₋₆)烷基是指包含一至六个碳原子的烷基。所述的烷基是支链的或直链的。

5 本申请化合物中所述的原子包括其同位素，例如，氢可以是氕或氘。

“烷基”是指直链或带有支链的，单价的，饱和脂肪链，包括但不限于如甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、戊基、异戊基、己基以及其它类似基团。优选 C₁₋₈ 烷基。更优选 C₁₋₆ 烷基。更优选 C₁₋₄ 烷基。

“环烷基”是指饱和的单环或多环烷基，可能与其它基团组合。环烷基包括但不限于
10 如环丙基、环丁基、环戊基、环己基、环庚基。优选 C₃₋₈ 环烷基。更优选 C₃₋₆ 环烷基。更优选 C₃₋₄ 环烷基。

“烷氧基”是指与一氧原子键合的直链或带有支链的，单价的，饱和脂肪链，包括但不限于如甲氧基、乙氧基、丙氧基、丁氧基、异丁氧基、叔丁氧基以及其它类似基团。优选 C₁₋₈ 烷氧基。更优选 C₁₋₆ 烷氧基。更优选 C₁₋₄ 烷氧基。

15 “卤素”是指氟，氯，溴和碘，优选氟和氯。

“卤代烷基”是指本文定义的烷基，其中一个或多个氢已经被相同或不同卤素替换。例举性的卤代烷基包括-CH₂Cl，-CH₂CF₃，-CH₂CCl₃，全氟烷基(例如，-CF₃)等。

“杂环基”是指非芳族单环基团，其中带有选自 N，O，或 S 的杂原子，其余环原子是 C。杂环基部分的实例包括但不限于：吡啶基，哌嗪基，高哌嗪基，吡咯烷基，吡唑烷基，
20 咪唑烷基，咪唑啉基，吗啡啉基，吡啶基，哒嗪基，嘧啶基，噁唑烷基，异噁唑烷基，噻唑烷基，异噻唑烷基，奎宁环基，噻二唑烷基，二氢呋喃基，四氢呋喃基，二氢吡喃基，四氢吡喃基，硫代吗啉基，硫代吗啉基亚砷，硫代吗啉基砷等。优选 4-7 元杂环基。更优选 4-6 元杂环基。

一个环状基团可通过多种方式与另一基团键合。如果未明确键合方式，则表示包括
25 所有可能的方式。例如，“吡啶基”包括 2-、3-、或 4-吡啶基，而“噻吩基”包括 2-或 3-噻吩基。

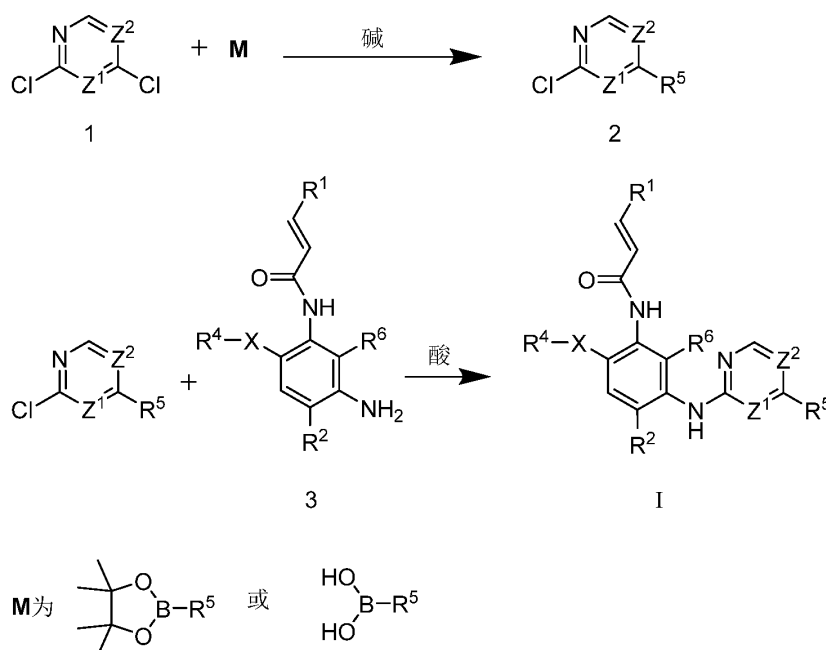
“药用盐”指常规的酸加成盐或碱加成盐，其保留式 I 化合物的生物有效性和性质，其由适宜的非毒性有机或无机酸或有机或无机碱形成。酸加成盐的例子包括衍生自无机酸和衍生自有机酸的那些盐，所述无机酸例如氢氯酸、氢溴酸、氢碘酸、硫酸、氨基磺酸、
30 磷酸和硝酸，所述有机酸例如对-甲苯磺酸、水杨酸、甲磺酸、草酸、琥珀酸、柠檬酸、

马来酸、乳酸、富马酸等。碱加成盐的例子包括衍生自铵、钾、钠和季铵氢氧化物的盐，例如氢氧化四甲铵。将药用化合物(即药物)化学改性成盐是药剂师公知的技术，用以获得化合物的改善的物理和化学稳定性、吸湿性、流动性和溶解性。

作为 EGFR 激酶抑制剂的化合物的制备方法

- 5 本申请还涉及制备式 I 化合物的方法。本发明的化合物可以由任何常规手段制备。实施例中提供了合成这些化合物的合适的方法。在多步骤合成路线中，反应的次序在特定情况下是可以调整的。

在某些实施方式中，本申请提供了一种制备式 I 化合物的方法，包括使化合物 1 与化合物 M 在碱性条件下反应，形成化合物 2，然后再使化合物 2 与化合物 3 在酸性条件下反应形成式 I 化合物的步骤；

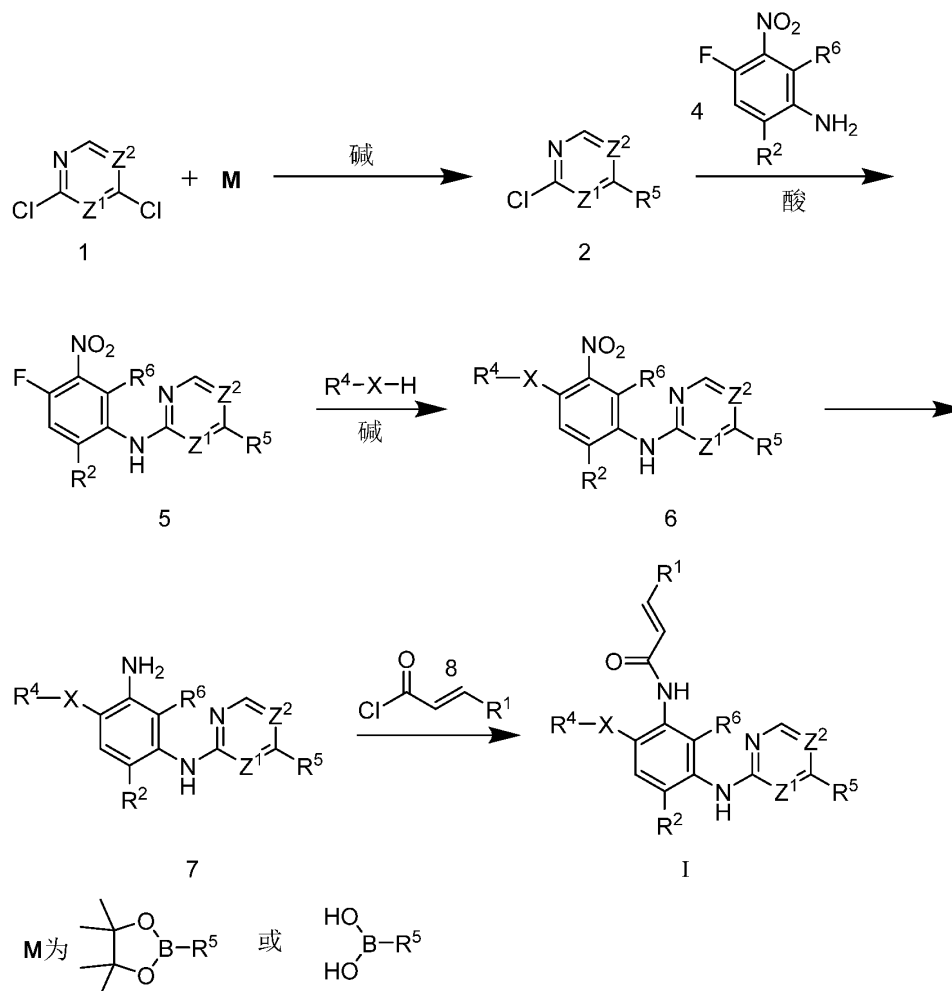


其中 R^1 、 R^2 、 R^4 、 R^5 、 R^6 、 X 、 Z^1 和 Z^2 如前述所定义。

- 15 优选地，所述碱为碳酸钠或碳酸氢钠；
 优选地，所述酸为甲磺酸或对甲苯磺酸。
 在某些实施方式中，所述制备式 I 化合物的方法包括如下反应步骤：
 (1) 使化合物 1 与化合物 M 在碱性条件下反应，形成化合物 2；
 (2) 使化合物 2 与化合物 4 在酸性条件下反应形成化合物 5；
 20 (3) 使化合物 5 与 $\text{R}^4\text{-X-H}$ 在碱性条件下反应形成化合物 6；

(4) 将化合物 6 还原为化合物 7;

(5) 使化合物 7 与化合物 8 反应, 形成式 I 所示的化合物;



5

其中 R^1 、 R^2 、 R^4 、 R^5 、 R^6 、X、 Z^1 和 Z^2 如前述所定义。

优选地, 在步骤 (1) 中, 所述碱为碳酸钠或碳酸氢钠;

优选地, 在步骤 (2) 中, 所述酸为甲磺酸或对甲苯磺酸;

优选地, 在步骤 (3) 中, 所述碱选自二异丙基乙胺, 碳酸钠和三乙胺。

10 作为 EGFR 激酶抑制剂的化合物药物组合物

本发明还提供了包括所述作为 EGFR 激酶抑制剂的化合物以及药学上可接受的载体或赋形剂的药物组合物。

在此提到的术语“药学上可接受的载体”是指一种药学上可接受的物质, 成分或者介质, 比如液体或固体填充剂, 稀释剂, 赋形剂, 溶剂或灌封材料, 其参与将本发明涉及

的化合物从某一位置，体液，组织，器官（内部或外部），或身体部分装载或传递到另一位置，体液，器官（内部或外部），或身体部分。药学上可接受的载体可以是介质，稀释剂，赋形剂或者其它没有过度毒性或者副作用并能用于接触动物组织的材料。典型的药学上可接受的载体包括糖类，淀粉，纤维素类，麦芽糖，黄耆胶，明胶，林格氏溶液，

5 海藻酸，生理盐水，缓冲剂等。

每种药学上可接受的载体应该与其它组成成分相容，例如与本发明中提供的结合物形成制剂，对生物活体组织或者器官没有过度毒性、刺激、过敏性反应、免疫原性或其它问题或并发症，且有较合理的效益风险比。

一些药学上可接受的载体的物质包括：（1）糖类，比如乳糖，葡萄糖和蔗糖；（2）
10 淀粉，比如玉米淀粉和马铃薯淀粉；（3）纤维素和其衍生物，比如羧甲基纤维素钠，乙基纤维素，醋酸纤维素；（4）西黄耆胶粉；（5）麦芽糖；（6）明胶；（7）滑石粉；（8）赋形剂，比如可可脂和栓剂蜡；（9）油类，比如花生油，棉籽油，红花油，芝麻油，橄榄油，玉米油和大豆油；（10）二醇类，比如丙二醇；（11）多元醇类，比如甘油，山梨醇，甘露醇和聚乙二醇；（12）脂类，比如油酸乙酯，月桂酸乙酯；（13）琼脂胶；（14）
15 缓冲剂，比如氢氧化镁和氢氧化铝；（15）海藻酸；（16）灭菌无热原水；（17）生理盐水；（18）林格氏溶液；（19）醇类，比如乙醇和丙醇；（20）磷酸缓冲液；（21）其它在药剂型中无毒性可相容的物质，比如丙酮。

药物组合物可能包括药学上可接受的辅料，以模拟生理条件，比如 pH 调节和缓冲剂，毒性调节剂等等，如乙酸钠，氯化钠，氯化钾，氯化钙，乳酸钠等。

20 药物成分可制成任何合适的剂型，如固体剂型（例如片剂，胶囊，粉末，颗粒等）和液体剂型（例如水溶液，乳浊液，酏剂，糖浆等）。药物组合物的制备方法工艺已众所周知，可根据常规工艺进行制备，比如在 Remington, The Science and Practice of Pharmacy (Gennaro ed. 20th edition, Williams & Wilkins PA, USA) (2000)中提供。

在某些实施方式中，本发明中提供的化合物或药物组合物可以被制成适于药物释放
25 的剂型，通过注射途径给药（如皮下，静脉，肌肉，动脉，鞘膜，囊内，框内，心脏内，真皮内，腹膜内，经气管，表皮，关节内，囊下，蛛网膜下，脊柱内，胸骨内，和/或输液）和非注射途径给药（如口服，肠道，口腔，鼻，鼻内，粘膜，表皮，贴膏剂，真皮，眼药，肺部，舌下，直肠，阴道或表皮局部给药）。

合适的剂型包括（但不局限于）注射用途的剂型比如乳状液，溶液和混悬液，口服
30 用途的剂型如片剂，胶囊，丸剂，糖衣丸，粉末和颗粒，局部用药或经皮肤吸收的剂型

如喷剂，软膏，糊剂，乳霜，洗剂，凝胶，溶液，药物贴片和吸入剂，阴道或直肠给药的剂型如栓剂。这些剂型可根据化合物以及合适的赋形剂在合适条件下制备，制备方法及工艺众所周知，比如由 Remington: 在 The Science and Practice of Pharmacy (Gennaro ed. 20th edition, Williams & Wilkins PA, USA) (2000) 提供。

- 5 在某些实施方式中，本申请提供了包含上述化合物以及药学上可接受的载体或赋形剂的药物组合物。在某些实施方式中，药物组合物为片剂、胶囊剂、丸剂、颗粒剂、散剂、栓剂、注射剂、溶液剂、混悬剂、膏剂、贴剂、洗剂、滴剂、擦剂、喷雾剂

作为 EGFR 激酶抑制剂的化合物药物组合物的应用

- 本发明的另一个方面提供了上述化合物和/或药物组合物在制备药物以及治疗疾病
10 中的应用。

在某些实施方式中，本发明提供了上述化合物和/或药物组合物在制备抗肿瘤的药物的应用。

- 在某些实施方式中，本申请提供了包含上述化合物和/或药物组合物在制备抗肿瘤药物中的应用。在某些实施方式中，所述抗肿瘤药物应用于以下病症：头颈部癌，黑色素
15 瘤，膀胱癌，食道癌，间变性大细胞淋巴瘤，肾细胞癌，乳腺癌，结肠直肠癌，卵巢癌，宫颈癌，胰腺癌，胶质瘤，胶质母细胞瘤，前列腺癌，白血病，淋巴瘤，非霍奇金淋巴瘤，胃癌，肺癌，肝细胞癌，胃肠道基质瘤，甲状腺癌，胆管癌，子宫内膜癌，多发性骨髓瘤或间皮瘤。

- 在某些实施方式中，本申请提供了一种治疗主体中肿瘤的方法，包括向所述主体给
20 予有效量的上述化合物或药物组合物，所述的主体优选哺乳动物，所述哺乳动物优选人。在某些实施方式中，给药方式包括口腔、粘膜、舌下、眼部、局部、肠道外、直肠、脑池、阴道、腹膜、膀胱、鼻部给药。

- 本发明涉及的化合物或药物组合物可通过任何合适的途径进入生物体内，比如通过口服，静脉注射，鼻内，外用，肌注，真皮内注射，经皮给药或皮下途径。在某些实施
25 方式中，本发明涉及的化合物或药物组合物的给药方式包括口腔、粘膜、舌下、眼部、局部、肠道外、直肠、脑池、阴道、腹膜、膀胱、鼻部给药。

- 在某些实施方式中，本发明涉及的结合物或药物组合物可以与第二活性物质同时进行施用，这样能在生物体内达到叠加甚至协同的作用。例如，本发明涉及的化合物可以和第二活性物质组合成一个药物组合物，或者以单独的组合物同时施用，或者以单独的
30 组合物依次施用。能与本发明化合物同时施用、用于治疗癌症的第二活性物质包括但不

局限于：氟尿嘧啶，阿霉素，柔红霉素，它莫西芬，亮丙瑞林，戈舍瑞林，氟他米特，尼鲁米特，非那雄胺，地塞米松，氨鲁米特，安吡啶、阿那曲唑，天冬酰胺酶，卡介苗，比卡鲁胺、博来霉素、临床、白消安，喜树碱，卡培他滨，卡铂，卡莫司汀，苯丁酸氮芥，顺铂，克拉屈滨，秋水仙碱，环磷酰胺、药物、环丙孕酮、阿糖胞苷、达卡巴嗪，
5 放线菌素 d，正定霉素，双烯雌酚、己烯雌酚、多西紫杉醇、阿霉素，亚德里亚霉素、表柔比星、雌二醇，雌氮芥、依托泊苷、依西美坦，非格司亭，氟达拉滨，氟氢可的松、氟尿嘧啶、氟甲睾酮、氟他米特，吉西他滨，染料木黄酮，戈舍瑞林，三苯氧胺、替尼泊苷、睾酮、二氯化二茂钛，拓普泰康，曲妥单抗、维甲酸、长春花碱、羟基脲，伊达比星，异环磷酰胺、伊马替尼、干扰素、伊立替康，伊立替康、来曲唑、甲酰四氢叶酸，
10 喷司他丁，光神霉素、甲基苄肼、雷替曲塞吡菲尔，利妥昔链脲菌素，苏拉明，亮丙瑞林、左旋咪唑，环己亚硝脲、氮芥、甲羟孕酮、甲地孕酮，美法仑、巯嘌呤、巯乙磺酸钠、甲氨蝶呤、丝裂霉素、米托坦、米托蒽醌，尼鲁米特，诺考达唑、奥曲肽、铂、紫杉醇、帕米磷酸，硫鸟嘌呤，三胺硫磷、氯甲烷、拓扑替康二茂钛，曲妥单抗，维甲酸、长春花碱，长春新碱、长春地辛，长春瑞滨。

15 在某些实施方式中，本发明提供的结合物可与非化学方法同时使用进行癌症治疗。在某些实施方式中，本发明提供的结合物可与放射疗法同时进行。在某些实施方式中，本发明提供的结合物可与外科手术，肿瘤热治疗，超声聚焦疗法，冷冻疗法或以上几种疗法结合使用。

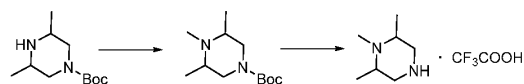
在某些实施方式中，本发明提供的结合物可与类固醇同时使用。合适的类固醇包括
20 但不局限于：安西缩松、倍氯米松，倍他米松，布地奈德，氯泼尼松，氯倍他索，皮质甾酮，可的松，羟泼尼缩松，去羟米松，地塞米松，双氟拉松，双氟米松，二氟孕甾丁酯，甘草次酸，氟扎可松，氟米松，氟尼缩松，氟氯奈德，肤轻松醋酸酯，氟轻松醋酸酯，氟可丁丁酯，氟可龙，丙酮缩氟氢羟龙，醋酸氟培龙，醋酸氟泼尼定，氟泼尼龙，氟氢缩松，丙酸氟、醛基缩松，丙酸氯倍他索，哈西缩松，卤米松，氢化可的松，氯替
25 波诺碳酸乙酯，甲哌地强龙，甲羟松，甲泼尼松，6-甲氢化泼尼松，在任糠酸盐，帕拉米松，泼尼松龙，地塞米松，和 25-二乙胺醋强的松龙。

在某些实施方式中，本发明提供的化合物可与免疫治疗剂同时使用。合适的免疫治疗剂包括：肿瘤细胞多药耐药性逆转剂（比如维拉帕米），雷帕霉素，霉酚酸酯，沙利度胺，环磷酰胺，环孢霉素，和单克隆抗体类。

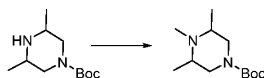
具体实施方式

实施例 1

1,2,6-三甲基哌嗪三氟乙酸盐的制备

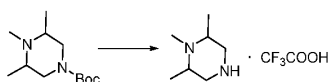


5 第一步：3,4,5-三甲基哌嗪-1-甲酸叔丁酯



氩气保护下，于 100 mL 三口瓶中加入 3,5-二甲基哌嗪-1-甲酸叔丁酯 (520 mg, 2.43 mmol) 和 THF (10 mL)，降温至 0 °C 左右，加入 NaH (70 mg, 2.91 mmol)，保温搅拌半小时，滴加 CH₃I (690 mg, 4.86 mmol) 的 THF (1 mL) 溶液。滴毕保温搅拌 1 小时，
 10 升至室温继续搅拌反应。TLC 监测反应，反应完毕后，加入 50 mL 纯化水，30 mL 乙酸乙酯，搅拌分液，水相用乙酸乙酯 (30 mL × 2) 萃取 2 次，合并有机相，饱和食盐水 (50 mL × 2) 洗 2 次，无水硫酸钠干燥，过滤，母液减压浓缩得 510 mg 产品。

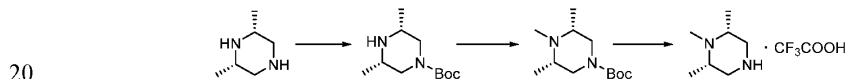
第二步：1,2,6-三甲基哌嗪三氟乙酸盐



15 于 100 mL 单口瓶中依次加入 3,4,5-三甲基哌嗪-1-甲酸叔丁酯，二氯甲烷 (10 mL) 和三氟乙酸 (4 mL)，室温搅拌反应，TLC 监测反应，反应完毕后，将反应液减压浓缩得 1,2,6-三甲基哌嗪三氟乙酸盐 870 mg (理论 280 mg)。

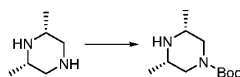
实施例 2

顺式-1,2,6-三甲基哌嗪三氟乙酸盐的制备



20

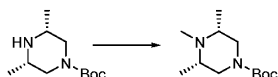
第一步：顺式-3,5-二甲基哌嗪-1-甲酸叔丁酯



于 100 mL 单口瓶中加入顺式-2,6-二甲基哌嗪 (1.0 g, 8.76 mmol) 和二氯甲烷 (20 mL), 降温至 0-5 °C。加入三乙胺 (2.22 g, 21.89 mmol), 滴加(Boc)₂O (1.92 g, 8.76 mmol) 的二氯甲烷 (10 mL) 溶液, 滴毕, 升温到室温搅拌过夜。TLC 监测反应, 反应完后,

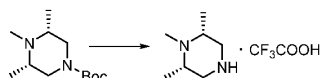
- 5 将反应液减压浓缩, 柱层析纯化, 洗脱液: DCM/MeOH = 30/1, 收集产品减压浓缩得 1.9 g。

第二步: 顺式-3,4,5-三甲基哌嗪-1-甲酸叔丁酯



以顺式-3,5-二甲基哌嗪-1-甲酸叔丁酯和 CH₃I 为原料, 制备过程参见实施例 1 第一步。

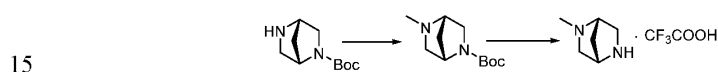
10 第三步: 顺式-1,2,6-三甲基哌嗪三氟乙酸盐合成



以顺式-3,4,5-三甲基哌嗪-1-甲酸叔丁酯为原料, 制备过程参见实施例 1 第二步。

实施例 3

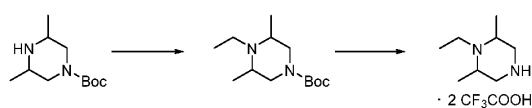
(1S,4S)-2-甲基-2,5-二氮杂双环[2.2.1]庚烷三氟乙酸盐的制备



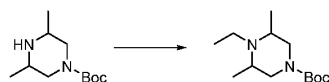
以(1S,4S)-2,5-二氮杂双环[2.2.1]庚烷-2-羧酸叔丁酯和 CH₃I 为起始原料, 制备过程参见实施例 1。

实施例 4

1-乙基-2,6-二甲基哌嗪三氟乙酸盐的制备



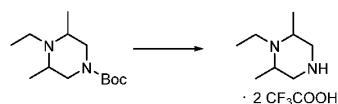
第一步：4-乙基-3,5-二甲基哌嗪-1-羧酸叔丁酯



以 3,5-二甲基哌嗪-1-甲酸叔丁酯和 C_2H_5I 为原料，DMF 为溶剂，80 °C 反应 7-8 h。

5 制备过程参见实施例 1 第一步。

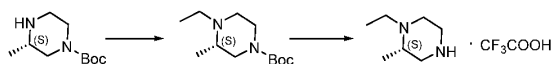
第二步：1-乙基-2,6-二甲基哌嗪三氟乙酸盐



以 4-乙基-3,5-二甲基哌嗪-1-羧酸叔丁酯原料，合成过程参见实施例 1 第二步。

实施例 5

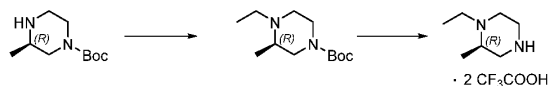
10 (S)-1-乙基-2-甲基哌嗪三氟乙酸盐的制备



以 (S)-3-甲基哌嗪-1-甲酸叔丁酯和 C_2H_5I 为原料，制备过程与实施例 1 相同。

实施例 6

(R)-1-乙基-2-甲基哌嗪三氟乙酸盐的制备

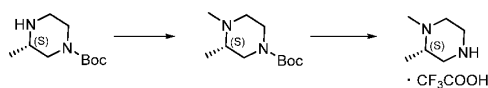


15

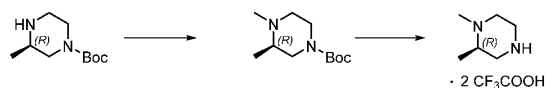
以 (R)-3-甲基哌嗪-1-甲酸叔丁酯和 C_2H_5I 为原料，DMF 为溶剂，制备过程参见实施

例 1。

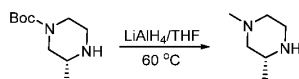
实施例 7

(S)-1,2-二甲基哌嗪三氟乙酸盐的制备

以(S)-3-甲基哌嗪-1-甲酸叔丁酯为原料, 制备过程参见实施例 1。

实施例 8**5 (R)-1,2-二甲基哌嗪三氟乙酸盐的制备**

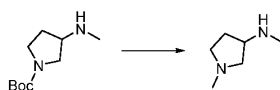
以(R)-3-甲基哌嗪-1-甲酸叔丁酯为原料, 制备过程参见实施例 1。

实施例 9**(R)-1,3-二甲基哌嗪的制备**

10

氩气保护下, 向 250 mL 三口瓶中加入四氢铝锂 (1.36 g, 36 mmol) 降温至 0 °C 左右, 滴加 THF (100 mL), 滴毕, 然后滴加(R)-3-甲基哌嗪-1-甲酸叔丁酯 (3.60 g, 18 mmol) 的 THF (10 mL) 溶液, 控制温度在 -5 ~ 0 °C, 滴毕, 升温至 60 °C 回流反应 2 h。TLC 监控反应。原料反应完全, 降温至 0 °C 左右, 依次缓慢滴加水 (1.37 mL), 氢氧化钠水溶液 (2 N, 1.37 mL), 水 (2.74 mL) 淬灭反应, 搅拌 5 min, 过滤, 滤饼用 15 mL 甲醇淋洗, 滤液 40 °C 减压浓缩, 得 2 g 无色油状物。粗品经柱层析纯化, 以中性氧化铝为吸附剂, 以 DCM/MeOH = 20/1 洗脱, 收集产品并浓缩, 得 1.3 g 无色油状物, 收率: 65%。

15

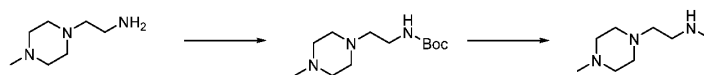
实施例 10**N,1-二甲基吡咯烷-3-胺的制备**

20

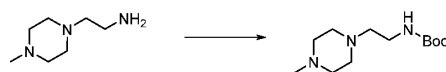
以 3-(甲基氨基)吡咯烷-1-羧酸叔丁酯为原料, 制备过程参见实施例 9。

实施例 11

N-甲基-2-(4-甲基哌嗪-1-基)乙-1-胺的制备



5 第一步: 叔丁基甲基(2-(4-甲基哌嗪-1-基)乙基)氨基甲酸酯



- 于 100 mL 三口瓶中加入 2-(4-甲基哌嗪-1-基)乙-1-胺 (1.0 g, 6.98 mmol) 和 DCM (15 mL)。冰浴降温至 0 °C。加入三乙胺 (1.41 g, 13.96 mmol), 搅拌 0.5 h, 然后滴加 (Boc)₂O (1.53 g, 6.98 mmol) 的 DCM (5 mL) 溶液, 滴毕后升温至室温搅拌反应。TLC
- 10 监控反应。反应完毕后, 将反应液减压浓缩干, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 30/1, 收集产品并减压浓缩得 1.4 g。

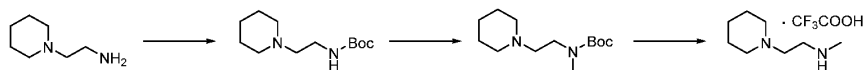
第二步: N-甲基-2-(4-甲基哌嗪-1-基)乙-1-胺



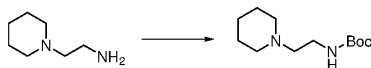
- 以叔丁基甲基(2-(4-甲基哌嗪-1-基)乙基)氨基甲酸酯为原料, 制备过程参见实
- 15 施例 9。

实施例 12

N-甲基-2-(哌啶-1-基)乙胺三氟乙酸盐的制备



第一步: (2-(哌啶-1-基)乙基)氨基甲酸叔丁酯



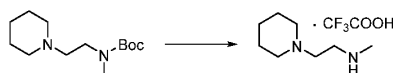
氩气保护下，于 100 mL 单三口瓶中加入 1-(2-氨基乙基)哌啶 (500 mg, 3.84 mmol) 和 THF (10 mL)，降温至 0-5 °C，滴加(Boc)₂O (1.05 g, 4.81 mmol) 的 THF (2 mL) 溶液，滴毕后升温到室温搅拌反应。TLC 监测反应，反应完后，加入 50 mL 纯化水，50 mL 乙酸乙酯，搅拌分液，水相用乙酸乙酯 (40 mL) 萃取 1 次，合并有机相，饱和食盐水 (50 mL × 2) 洗 2 次，无水硫酸钠干燥 30 min，过滤，滤液浓缩得 891 mg 产品。

第二步：甲基 (2- (哌啶-1-基) 乙基) 氨基甲酸叔丁酯



氩气保护下，于 100 mL 三口瓶中加入 DMF (10 mL) 和 NaH (220 mg, 5.50 mmol)，冰盐浴降温至 0-5 °C 左右，滴加 (2- (哌啶-1-基) 乙基) 氨基甲酸叔丁酯 (890 mg, 3.67 mmol) 的 DMF (5 mL) 溶液，滴加完毕后保温搅拌 1 h。然后滴加 CH₃I (780 mg, 5.50 mmol) 的 DMF (1 mL) 溶液。滴加完毕后保温搅拌 1 h，升温至室温反应 1 d。TLC 监测反应，反应完全后加入 50 mL 氯化铵水溶液，40 mL 乙酸乙酯，搅拌分液，水相用乙酸乙酯 (30 mL × 2) 萃取 2 次，合并有机相，饱和食盐水 (50 mL × 2) 洗 2 次，无水硫酸钠干燥 30 min，过滤，滤液减压浓缩得粗品。粗品经柱层析纯化，洗脱液：DCM/MeOH = 30/1，收集产品，减压浓缩得 140 mg。

第三步：N-甲基-2- (哌啶-1-基) 乙胺三氟乙酸盐

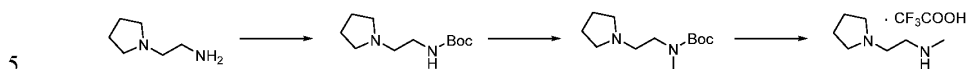


于 100 mL 单口瓶中依次加入甲基 (2- (哌啶-1-基) 乙基) 氨基甲酸叔丁酯 (130 mg, 0.54 mmol)，二氯甲烷 (3 mL) 和三氟乙酸 (2 mL)，室温搅拌反应，TLC 监测反应，反

应完毕后, 将反应液减压浓缩得 148 mg N-甲基-2-(吡咯烷-1-基)乙胺三氟乙酸盐, 产品无需纯化, 直接用于下一步合成。

实施例 13

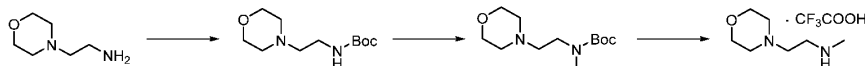
N-甲基-2-(吡咯烷-1-基)乙胺三氟乙酸盐的制备



以 1-(2-氨基乙基)吡咯烷为原料, 制备过程参见实施例 12。

实施例 14

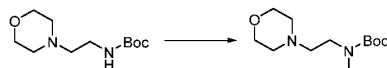
N-甲基-2-吗啉乙-1-胺三氟乙酸盐的制备



10 第一步: (2-吗啉乙基)氨基甲酸叔丁酯

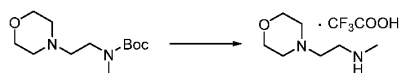
氩气保护下, 于 100 mL 单三口瓶中依次加入 1-(2-氨基乙基)吗啉 (500 mg, 3.84 mmol), 二氧六环 10 mL, 碳酸钠 (814 mg, 7.68 mmol) 和水 (2 mL), 冰盐浴降温至 0℃。滴加 (Boc)₂O (992 mg, 4.55 mmol) 的二氧六环 (1 mL) 溶液, 滴毕后搅拌反应。TLC 监测反应, 反应完全后, 加入纯化水 (50 mL), 乙酸乙酯 (40 mL), 搅拌分液, 水相用乙酸乙酯 (40 mL) 萃取 1 次, 合并有机相, 饱和食盐水 (50 mL × 2) 洗 2 次, 无水硫酸钠干燥 30min, 过滤, 滤液减压浓缩得 885 mg 产品。

第二步: 甲基(2-吗啉乙基)氨基甲酸叔丁酯



以 (2-吗啉乙基)氨基甲酸叔丁酯为原料, 制备过程参见实施例 12 第二步。

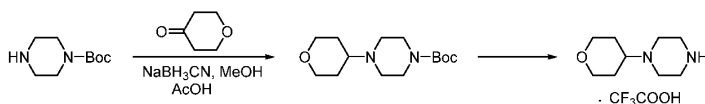
20 第三步: N-甲基-2-(吡咯烷-1-基)乙胺三氟乙酸盐



以甲基(2-吗啉乙基)氨基甲酸叔丁酯为原料, 制备过程参见实施例 12 第三步。

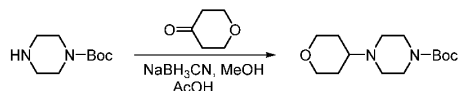
实施例 15

1-(四氢-2H-吡喃-4-基)哌嗪三氟乙酸盐的制备



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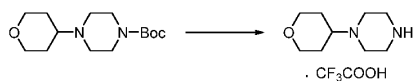
第一步: 4-(四氢-2H-吡喃-4-基)哌嗪-1-甲酸叔丁酯



向 100 mL 单口瓶中依次加入哌嗪-1-甲酸叔丁酯 (1.0 g, 5.37 mmol), 四氢-4H-吡喃-4-酮 (1.07 g, 10.7 mmol) 和甲醇 (20 mL), 分批加入氰基硼氢化钠 (507 mg, 8.06 mmol), 加毕, 加入 0.5 mL 醋酸, 室温搅拌反应 6-7 h。TLC 监测反应。反应完全后, 加入饱和碳酸氢钠水溶液淬灭反应, 水相用乙酸乙酯 (100 mL × 3) 萃取 3 次, 合并有机相, 浓缩。粗品经柱层析纯化, 用 DCM/MeOH = 20/1 洗脱, 收集产品并浓缩, 得到 1.5 g 无色油状物。

10

第二步: 1-(四氢-2H-吡喃-4-基)哌嗪三氟乙酸盐

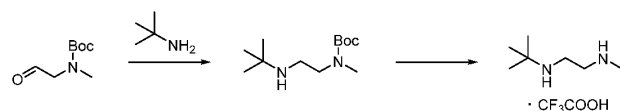


15

向 100 mL 单口瓶中依次加入 4-(四氢-2H-吡喃-4-基)哌嗪-1-甲酸叔丁酯 (1.5 g, 5.55 mmol) 和二氯甲烷 (20 mL), 搅拌下加入三氟乙酸 (6 mL), 加毕, 室温搅拌反应 2-3 h。TLC 监控反应。反应完全后, 浓缩。加入甲基叔丁基醚 (20 mL) 打浆 5 min, 过滤, 烘干, 得 1.75 g 白色固体。

实施例 16

N1-(叔丁基)-N2-甲基乙烷-1,2-二胺的制备

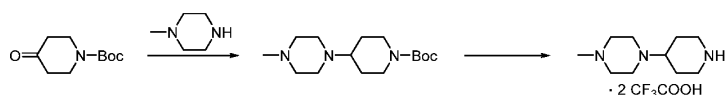


以 N-Boc-(甲胺基)乙醛和叔丁胺为原料, 三乙酰氧基硼氢化钠为还原剂, 氯仿为

5 溶剂, 制备过程参见实施例 15。

实施例 17

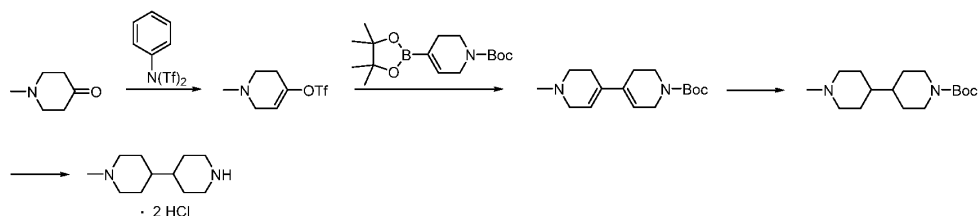
1-甲基-4-(哌啶-4-基)哌嗪三氟乙酸盐的制备



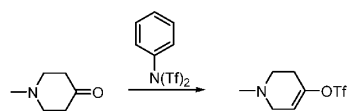
以 N-叔丁氧羰基-4-哌啶酮和 1-甲基哌嗪为原料, 制备过程参见实施例 15。

10 实施例 18

1-甲基-4,4'-联哌啶盐酸盐的制备



第一步: 三氟甲磺酸 1-甲基-1,2,3,6-四氢吡啶-4-基酯

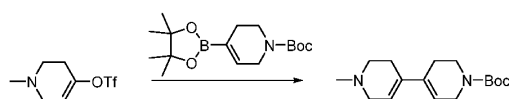


15 氩气保护下, 向 250 mL 三口瓶中加入 THF (30 mL), 降至-78 °C, 滴加 LDA (30.4 mL, 60.8 mmol), 控制温度在-78 °C, 滴加 1-甲基哌啶-4-酮 (4.0 mL, 30.4 mmol) 的 THF (10 mL) 溶液, 滴毕, 升温至-10 °C 反应 30 min。降至-78 °C, 滴加 N,N-双(三氟甲磺酰

基)苯胺 (16.29 g, 45.63 mmol) 的 THF (50 mL) 溶液, 加毕, 升至室温反应 1-2 h。TLC 监控反应。反应完全后, 反应液浓缩。粗品经柱层析纯化, 用 PE/EA=5/1 (中性氧化铝) 洗脱, 收集产品浓缩, 得 8.0 g 淡黄色油状物, 收率: 74.07%。

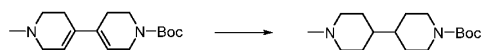
第二步: 1'-甲基-1',2',3,3',6,6'-六氢-(4,4'-联吡啶)-1(2H)-甲酸叔丁酯

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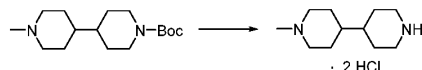
氩气保护下, 向 100 mL 单口瓶中依次加入三氟甲磺酸 1-甲基-1,2,3,6-四氢吡啶-4-基酯 (1.0 g, 4.08 mmol), N-叔丁氧羰基-1,2,5,6-四氢吡啶-4-硼酸频哪醇酯 (2.5 g, 8.1 mmol), 碳酸钠 (865 mg, 8.1 mmol), Pd(PPh₃)₄ (940 mg, 0.81 mmol), 甲苯 (24 mL), 乙醇 (4 mL) 和水 (4 mL), 加毕, 升至 120 °C 反应 7-8 h。TLC 监控反应。反应完全后, 加入 5 mL 水, 水相用乙酸乙酯 (100 mL × 3) 萃取 3 次, 合并有机相, 浓缩。粗品经柱层析纯化, 用 DCM/MeOH = 10/1 洗脱, 浓缩, 得 500 mg 淡黄色油状物, 收率: 44.24%。

第三步: 1'-甲基-(4,4'-联哌啶)-1-羧酸叔丁酯



向 100 mL 单口瓶中依次加入 1'-甲基-1',2',3,3',6,6'-六氢-(4,4'-联吡啶)-1(2H)-甲酸叔丁酯 (500 mg, 1.79 mmol) 和甲醇 (20 mL), 搅拌下加入 Pd/C (200 mg, 50%), 加毕, 室温加氢搅拌反应 14-16 h。过滤, 滤液浓缩, 得 450 mg 黄色油状物, 收率: 88.75%。

第四步: 1-甲基-4,4'-联哌啶盐酸盐



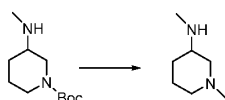
向 100 mL 单口瓶中依次加入 1'-甲基-(4,4'-联哌啶)-1-羧酸叔丁酯 (450 mg, 1.59 mmol) 和二氯甲烷 (10 mL), 搅拌下加入三氟乙酸 (5 mL), 加毕, 室温搅拌反应 2-3 h。反应

液浓缩。向剩余物中加入甲基叔丁基醚 (20 mL) 和浓盐酸 (2 mL), 浓缩, 得到 380 mg 类白色固体, 收率: 93.82%。

实施例 19

N, 1'-二甲基哌啶-3-胺的制备

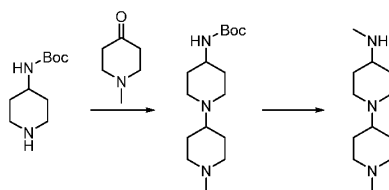
5



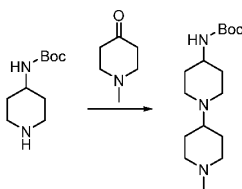
以 3-(甲基氨基)哌啶-1-甲酸叔丁酯为原料, 制备过程参见实施例 9。

实施例 20

N, 1'-二甲基-[1, 4'-联哌啶]-4-胺的制备

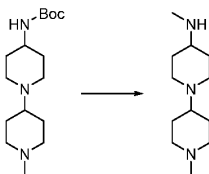


10 第一步: (1'-甲基-[1, 4'-联哌啶]-4-基)氨基甲酸叔丁酯



以哌啶-4-基氨基甲酸叔丁酯和 1-甲基-哌啶-4-酮为原料, 制备过程参见实施例 15 第一步。

第二步: N, 1'-二甲基-[1, 4'-联哌啶]-4-胺

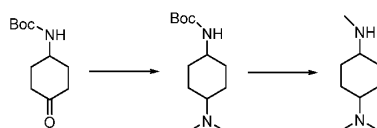


15

以 (1'-甲基-[1, 4'-联哌啶]-4-基) 氨基甲酸叔丁酯为原料, 制备过程参见实施例 9。

实施例 21

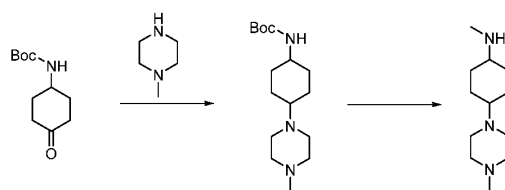
N1, N1, N4-三甲基-环己烷-1, 4-二胺的制备



- 5 以 (4-氧代环己基) 氨基甲酸叔丁酯和二甲胺盐酸盐为原料, 制备过程参见实施例 20。

实施例 22

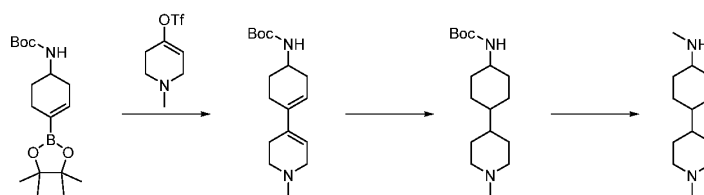
N-甲基-4-(4-甲基哌嗪-1-基) 环己-1-胺



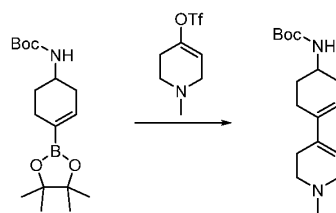
- 10 以 (4-氧代环己基) 氨基甲酸叔丁酯和 1-甲基哌嗪为原料, 制备过程参见实施例 20。

实施例 23

N-甲基-4-(1-甲基哌啶-4-基) 环己烷-1-胺

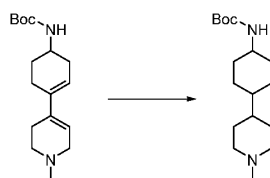


第一步: (4-(1-甲基-1, 2, 3, 6-四氢吡啶-4-基) 环己-3-烯-1-基) 氨基甲酸叔丁酯



以 N-叔丁氧羰基环己-3-烯氨基-4-硼酸频哪醇酯和 1-甲基-1, 2, 3, 6-四氢吡啶-4-基三氟甲磺酸酯为原料, 制备过程参见实施例 18 第二步。

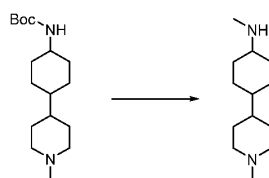
第二步: (4-(1-甲基吡啶-4-基)环己基)氨基甲酸叔丁酯



5

以 (4-(1-甲基-1, 2, 3, 6-四氢吡啶-4-基)环己-3-烯-1-基)氨基甲酸叔丁酯为原料, 制备过程参见实施例 18 第三步。

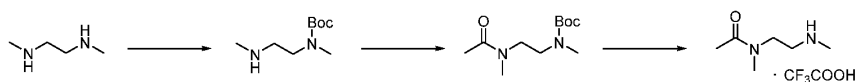
第三步: N-甲基-4-(1-甲基吡啶-4-基)环己烷-1-胺



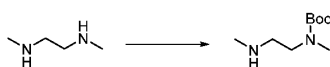
10 以 (4-(1-甲基吡啶-4-基)环己基)氨基甲酸叔丁酯为原料, 制备过程参见实施例 9。

实施例 24

N-甲基-N-(2-(甲基氨基)乙基)乙酰胺三氟乙酸盐



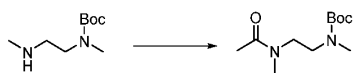
第一步: 甲基(2-(甲基氨基)乙基)氨基甲酸叔丁酯



15

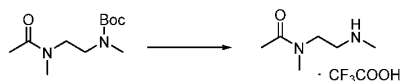
- 于 100 mL 的单口瓶中加入 N1, N2-二甲基乙-1, 2-二胺 (4 g, 45 mmol), 冰浴降温至 0 °C 左右, 然后滴加(Boc)₂O (5 g, 23 mmol) 的 DCM (20 mL) 溶液, 滴毕升温至 25 °C 搅拌反应 4 h。减压浓缩, 向剩余物中加饱和碳酸钠溶液, 用乙酸乙酯 (30 mL × 3) 萃取 3 次, 合并有机相, 用饱和食盐水 (20 mL × 3) 洗 3 次, 无水硫酸钠干燥 30 min,
- 5 减压抽滤, 滤液于 45 °C 减压浓缩得粗品。粗品经柱层析纯化, 用 DCM/MeOH = 30/1 洗脱, 收集产品, 减压浓缩得 2.1 g 黄色油状物。

第二步: 甲基 (2- (N-甲基乙酰氨基) 乙基) 氨基甲酸叔丁酯



- 于 100 mL 的三口瓶中依次加入甲基 (2- (甲基氨基) 乙基) 氨基甲酸叔丁酯 (2.15 g, 11.4 mmol), DCM (10 mL) 和三乙胺 (2.3 g, 23 mmol), 冰盐浴降温至 -5-0 °C, 缓慢滴加醋酸酐 (1.4 g, 14.7 mmol), 滴毕, 升温至 25 °C 搅拌反应 1 h。向反应体系中加入水 (20 mL), DCM (30 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水 (20 mL × 3) 洗 3 次, 无水硫酸钠干燥 30 min, 减压抽滤, 滤液于 45 °C 减压浓缩得粗品。粗品经柱层析纯化, 洗脱液: DCM/MeOH = 50/1, 收集产品, 减压浓缩得 2.3 g 黄色油状物。

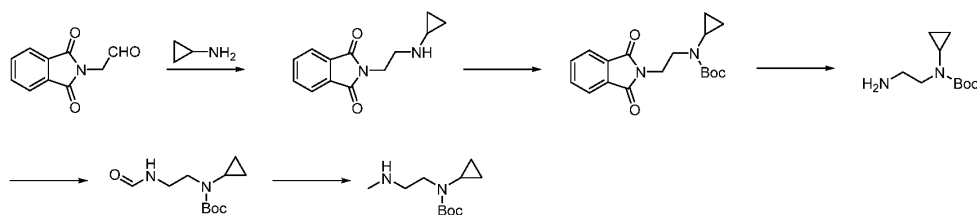
15 第三步: N-甲基-N- (2- (甲基氨基) 乙基) 乙酰胺三氟乙酸盐



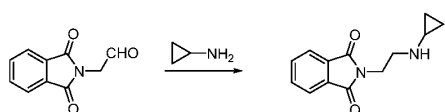
- 于 100 mL 单口瓶中依次加入甲基 (2- (N-甲基乙酰氨基) 乙基) 氨基甲酸叔丁酯 (2.4 g, 0.01 mol) 和 DCM (10 mL), 搅拌下滴加三氟乙酸 (3.0 g, 0.26 mol), 于 25 °C 搅拌反应 3 h。反应液于 50 °C 减压浓缩, 加入无水乙醇 (10 mL × 2) 浓缩 2 次, 向剩余物加入甲基叔丁基醚搅拌, 过滤, 滤饼减压干燥得 3.1 g 绿色油状物。

实施例 25

环丙基(2-(甲基氨基)乙基)氨基甲酸叔丁酯

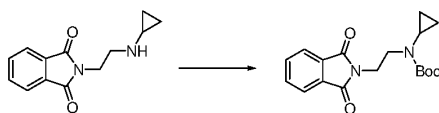


第一步: N-(2-(环丙基氨基)乙基)邻苯二甲酰亚胺



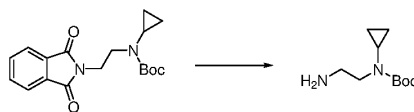
- 5 于 100 mL 单口瓶中依次加入 N-(2-乙醛基)邻苯二甲酰亚胺, 环丙胺(663 mg, 11.6 mmol)和氯仿(30 mL), 室温搅拌 1 h, 加入三乙氧基硼氢化钠(6.73 g, 31.7 mmol), 加毕室温反应 5-6 h。加入饱和碳酸氢钠溶液调 pH>8, 水相用 DCM (100 mL × 3) 萃取 3 次, 合并有机相, 减压浓缩的粗品。粗品经柱层析纯化, 洗脱液: DCM/MeOH = 50/1, 收集产品, 减压浓缩得 1.0 g 淡黄色固体, 收率: 28.7%。

10 第二步: 环丙基(2-(邻苯二甲酰亚胺-2-基)乙基)氨基甲酸叔丁酯



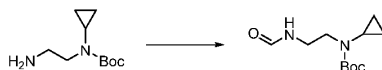
- 于 100 mL 单口瓶中依次加入 N-(2-(环丙基氨基)乙基)邻苯二甲酰亚胺(1.0 g, 4.34 mmol), DCM(20 mL), DIPEA(616 mg, 4.78 mmol)和(Boc)₂O(1.04 g, 4.78 mmol)。25 °C 搅拌反应 3-4 h。向反应体系中加入水(50 mL), DCM (30 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水(20 mL × 3)洗 3 次, 无水硫酸钠干燥 30 min, 减压抽滤, 滤液于 45 °C 减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 50/1, 收集产品, 减压浓缩得 1.0 g 白色固体, 收率: 69.9%。

第三步: (2-氨基乙基)(环丙基)氨基甲酸叔丁酯



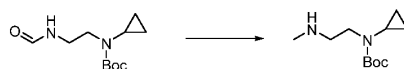
于 100 mL 的单口瓶中依次加环丙基 (2-(邻苯二甲酰亚胺-2-基)乙基)氨基甲酸叔丁酯 (1.0 g, 3.0 mmol) 和无水乙醇 (100 mL), 搅拌下加入水合肼 (1.89 g, 30 mmol),
 5 25 °C 搅拌反应 2-3 h。过滤, 滤液于 45 °C 减压浓缩, 得 700 mg 黄色油状物, 收率: 115%。

第四步: 环丙基 (2-甲酰氨基乙基) 氨基甲酸叔丁酯



于 100 mL 单口瓶中依次加入 (2-氨基乙基)(环丙基)氨基甲酸叔丁酯 (650 mg, 3.25 mmol) 和甲酸乙酯 (15 mL), 25 °C 搅拌反应 15 h。减压浓缩得 700 mg 黄色油状物,
 10 收率: 94.5%。

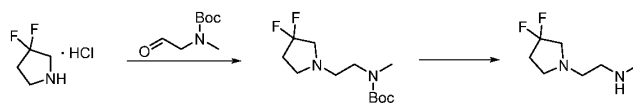
第五步: 环丙基 (2-(甲基氨基)乙基)氨基甲酸叔丁酯



氩气保护下, 于 100 mL 单口瓶中依次加入环丙基 (2-甲酰氨基乙基) 氨基甲酸叔丁酯 (700 mg, 3.07 mmol) 和四氢呋喃 (15 mL), 缓慢滴加 $\text{BH}_3(\text{Me}_2\text{S})$ (3 mL), 65 °C
 15 搅拌反应 3 h。降至室温, 减压浓缩。向剩余物中加入无水乙醇 (15 mL), 碳酸钾 (1.0 g), 25 °C 搅拌反应 15 h。过滤, 滤液减压浓缩, 向剩余物中加入水 (30 mL), 水相用乙酸乙酯 (50 mL $\times$ 3) 萃取 3 次, 合并有机相, 减压浓缩得粗品。粗品经柱层析纯化, 洗脱液: DCM/MeOH = 30/1, 收集产品, 减压浓缩得 210 mg 淡黄色油状物, 收率: 31.9%。

实施例 26

20 2-(3, 3-二氟吡咯烷-1-基)-N-甲基-1-胺



以甲基(2-氧代乙基)氨基甲酸叔丁酯和3,3-二氟吡咯烷盐酸盐为原料,制备过程参见实施例15。

实施例 27

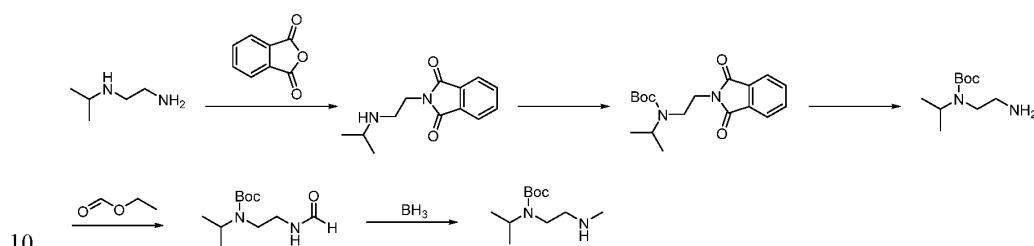
5 N-甲基-N-(3-(甲基氨基)丙基)乙酰胺三氟乙酸盐



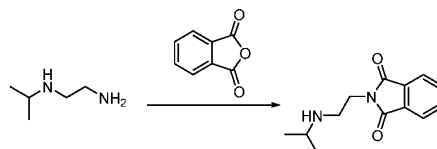
以N1,N3-二甲基丙烷-1,3-二胺为原料,制备过程参见实施例24。

实施例 28

异丙基(2-(甲基氨基)乙基)氨基甲酸叔丁酯

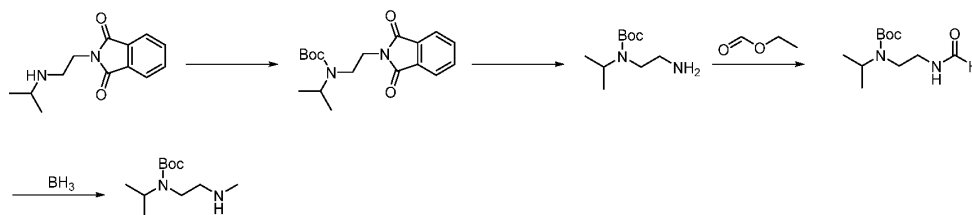


第一步: 2-(2-(异丙基氨基)乙基)邻苯二甲酰亚胺



于100 mL三口瓶中依次加入N-异丙基乙二胺,邻苯二甲酸酐(4.5 g, 0.03 mol),对甲苯磺酸(500 mg, 3 mmol)和甲苯(20 mL),升温至115 °C回流反应4h。降至室温,加入饱和碳酸氢钠溶液调pH>8,用乙酸乙酯(30 mL×3)萃取3次,合并有机相,饱和食盐水(20 mL×3)洗3次,无水硫酸钠干燥30 min,减压抽滤,滤液于45 °C减压浓缩,得4.2 g淡黄色油状物。

第二、三、四、五步：异丙基(2-(甲基氨基)乙基)氨基甲酸叔丁酯

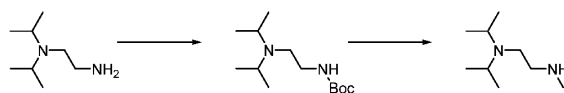


以 2-(2-(异丙基氨基)乙基)邻苯二甲酰亚胺为原料, 制备过程参见实施例 25 第

二、三、四、五步。

5 实施例 29

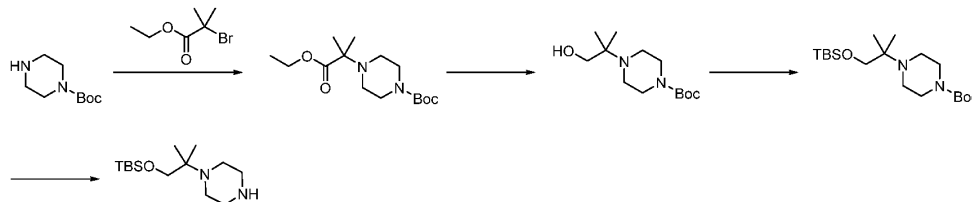
N1, N1 二异丙基-N2-甲基乙二胺



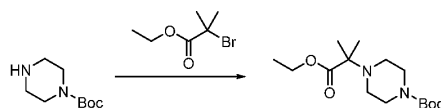
以 N1, N1-二异丙基乙二胺为原料, 制备过程参见实施例 11。

实施例 30

10 1-(1-((叔丁基二甲基硅烷基)氧基)-2-甲基丙-2-基)哌嗪



第一步：4-(1-乙氧基-2-甲基-1-氧代丙-2-基)哌嗪-1-甲酸叔丁酯

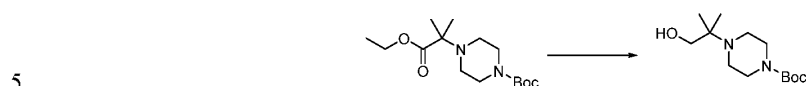


于 100 mL 单口瓶中依次加入哌嗪-1-甲酸叔丁酯 (2.5 g, 13.4 mmol), 碳酸钾 (2.78

15 g, 20.1 mmol) 和 DMF (60 mL), 搅拌 10 min, 然后加入 2-溴-2-甲基丙酸乙酯 (2.86 g,

14.7 mmol), 室温搅拌反应过夜。向反应体系中加入水 (100 mL), 水相用乙酸乙酯 (100 mL × 3) 萃取 3 次, 合并有机相, 减压浓缩得粗品。粗品经柱层析纯化, 洗脱液: DCM/MeOH = 30/1, 收集产品, 减压浓缩得 1.0 g 黄色油状物, 收率: 30.3%。

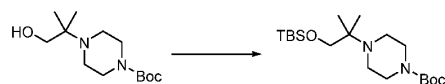
第二步: 4-(1-羟基-2-甲基丙-2-基)哌嗪-1-甲酸叔丁酯



氩气保护下, 于 100 mL 三口瓶中依次加入 4-(1-乙氧基-2-甲基-1-氧代丙-2-基)哌嗪-1-甲酸叔丁酯 (1.22 g, 4.06 mmol) 和四氢呋喃 (40 mL), 冰浴降至 0 °C, 滴加四氢铝锂 (310 mg, 8.13 mmol) 的四氢呋喃溶液, 0 °C 搅拌反应 2 h。加入饱和氯化铵水溶液, 水相用 DCM (100 mL × 2) 萃取 2 次, 合并有机相, 减压浓缩得粗品。粗品经柱层析 (中性氧化铝) 纯化, 洗脱液: DCM/MeOH = 20/1, 收集产品, 减压浓缩得 1.0 g 无色油状物, 收率: 96.2%。

10

第三步: (1-((叔丁基二甲基硅烷基)氧基)-2-甲基丙烷-2-基)哌嗪-1-甲酸叔丁酯

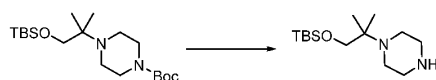


氩气保护下, 于 100 mL 单口瓶中依次加入 4-(1-羟基-2-甲基丙-2-基)哌嗪-1-甲酸叔丁酯 (780 mg, 3.02 mmol), 咪唑 (617 mg, 9.06 mmol) 和 DMF (20 mL), 搅拌溶解后, 加入叔丁基二甲基氯硅烷 (1.0 g, 6.04 mmol), 油浴升温至 80 °C 搅拌反应 4-5 h。降温至室温, 反应体系中加入水 (50 mL), 水相用乙酸乙酯 (80 mL × 3) 萃取 3 次, 合并有机相, 减压浓缩得粗品。粗品经柱层析纯化, 洗脱液: DCM/MeOH = 20/1, 收集产品, 减压浓缩得 1.4 g 淡黄色油状物, 收率: 125%。

15

第四步: 1-(1-((叔丁基二甲基硅烷基)氧基)-2-甲基丙-2-基)哌嗪

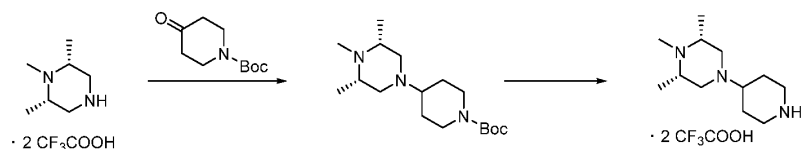
20



于 100 mL 单口瓶中依次加入 (1-((叔丁基二甲基甲硅烷基)氧基)-2-甲基丙烷-2-基)哌嗪-1-甲酸叔丁酯 (1.4 g, 3.76 mmol) 和 DCM (20 mL), 降温至 0 °C, 滴加三氟乙酸 (5 mL), 0 °C 搅拌反应 4-5 h。加入饱和碳酸钠水溶液调 pH>7, 水相用 DCM (80 mL × 3) 萃取 3 次, 合并有机相, 减压浓缩得 1.0 g 淡黄色油状物, 收率: 98.0%。

实施例 31

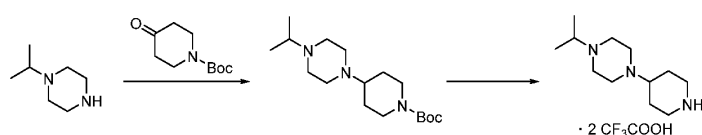
(2S, 6R)-1, 2, 6 三甲基-4-(哌啶-4-基)哌嗪三氟乙酸盐



以 (2R, 6S)-1, 2, 6-三甲基哌嗪三氟乙酸盐和 N-叔丁氧羰基-4-哌啶酮为原料, 制备过程参见实施例 15。

实施例 32

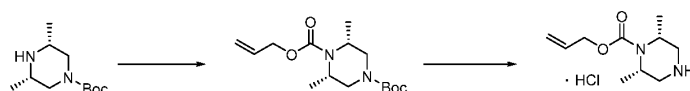
1-异丙基-4-(哌啶-4-基)哌嗪三氟乙酸盐



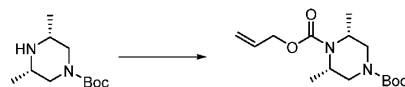
以 1-异丙基哌嗪和 N-叔丁氧羰基-4-哌啶酮为原料, 制备过程参见实施例 15。

实施例 33

(2R, 6S)-2, 6-二甲基哌嗪-1-甲酸烯丙酯盐酸盐

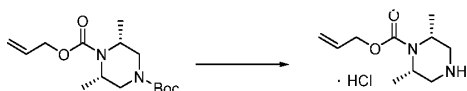


第一步: 4-(叔丁基)(2R, 6S)-2, 6-二甲基哌嗪-1, 4-二甲酸 1-烯丙酯



于 100 mL 三口瓶中依次加入顺式-3, 5-二甲基哌嗪-1-甲酸叔丁酯(2 g, 9.34 mmol), 吡啶(1.47 g, 18.6 mmol)和 DCM(10 mL), 降温至 0 °C, 滴加氯甲酸烯丙酯(1.68 g, 14 mmol)的 DCM 溶液, 升温至室温反应过夜。反应体系加入水(20 mL), 静置分层, 有机相浓缩得粗品。粗品经柱层析纯化, 洗脱剂: PE/EA = 5/1, 收集产品, 减压浓缩得 1.2 g 无色油状物, 收率: 43.2%。

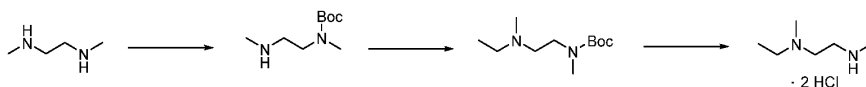
第二步: (2R, 6S)-2, 6-二甲基哌嗪-1-甲酸烯丙酯盐酸盐



于 100 mL 单口瓶中依次加入 4-(叔丁基)(2R, 6S)-2, 6-二甲基哌嗪-1, 4-二甲酸 1-烯丙酯(1.1 g, 3.69 mmol)和 DCM(10 mL), 搅拌下加入三氟乙酸(5 mL), 室温反应 2-3 h。减压浓缩。加入浓盐酸(1 mL)和乙醇(5 mL), 继续浓缩。向剩余物中加入异丙醚(10 mL)搅拌 10 min, 过滤, 滤饼干燥得 640 mg 黄色固体, 收率: 74.15%。

实施例 34

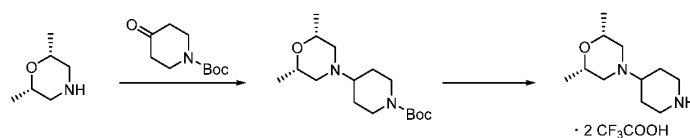
15 N1-乙基-N1, N2-二甲基乙二胺盐酸盐



以 N1, N2-二甲基乙二胺为原料, 制备过程参见实施例 2。

实施例 35

顺式-2, 6-二甲基-4-(哌啶-4-基)吗啉三氟乙酸盐



以顺式-2,6-二甲基吗啉和N-叔丁氧羰基-4-哌啶酮为原料,制备过程参见实施例 15。

实施例 36

3-((叔丁基二甲基硅烷基)氧基)-N-甲基丙-1-胺

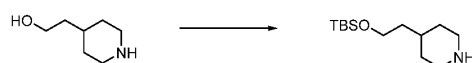
5



以 3-(甲基氨基)丙醇为原料,制备过程参见实施例 30 第三步。

实施例 37

4-(2-((叔丁基二甲基硅烷基)氧基)乙基)哌啶

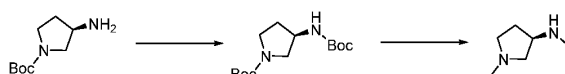


10

以 2-(哌啶-4-基)乙-1-醇为原料,制备过程参见实施例 30 第三步。

实施例 38

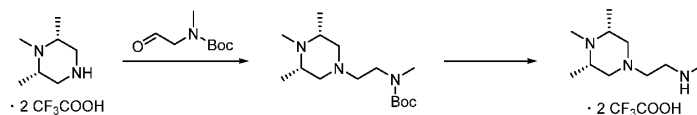
(R)-N, 1-二甲基吡咯烷-3-胺



以 (R)-3-氨基吡咯烷-1-甲酸叔丁酯为原料,制备过程参见实施例 11。

15 实施例 39

N-甲基-2-((3S, 5R)-3, 4, 5-三甲基哌嗪-1-基)乙胺三氟乙酸盐

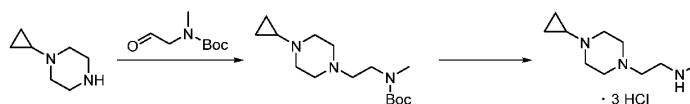


以 N-Boc-(甲胺基)乙醛和(2S, 6R)-1, 2, 6 三甲基哌嗪三氟乙酸盐为原料,制

备过程参见实施例 15。

实施例 40

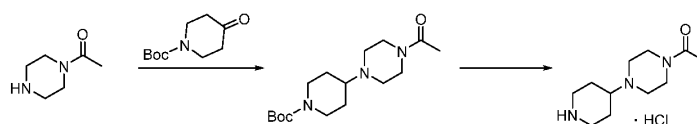
2-(4-环丙基哌嗪-1-基)-N-甲基乙胺盐酸盐



5 以 N-Boc-(甲胺基)乙醛和 1-环丙基哌嗪为原料, 制备过程参见实施例 15。

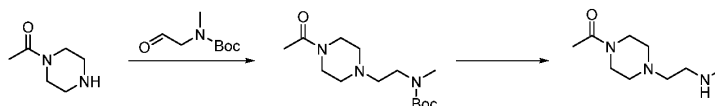
实施例 41

1-(4-(哌啶-4-基)哌嗪-1-基)乙-1-酮盐酸盐



以 1-(哌嗪-1-基)乙酮和 N-叔丁氧羰基-4-哌啶酮为原料, 制备过程参见实施例 15。

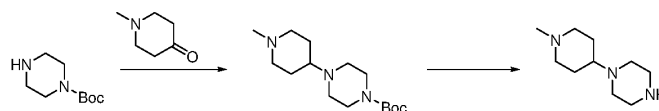
10 实施例 42



以 1-(哌嗪-1-基)乙酮和 N-Boc-(甲胺基)乙醛为原料, 制备过程参见实施例 15。

实施例 43

1-(1-甲基哌啶-4-基)哌嗪

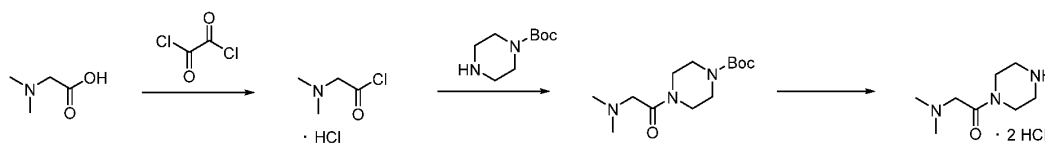


15

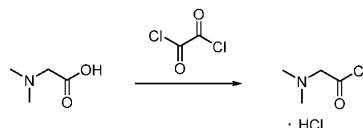
以 1-甲基-4-哌啶酮和哌嗪-1-甲酸叔丁酯为原料, 制备过程参见实施例 15。

实施例 44

2-(二甲基氨基)-1-(哌嗪-1-基)乙酮盐酸盐

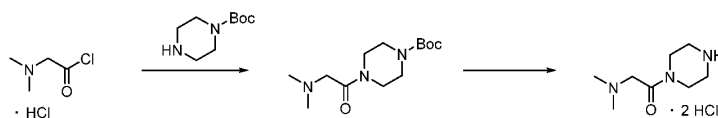


第一步: N, N-二甲氨基乙酰氯盐酸盐



- 5 氩气保护下, 于 100 mL 三口瓶中依次加入 N, N-二甲氨基甘氨酸 (1 g, 10 mmol), 乙腈 (15 mL) 和 DMF (5 d), 室温滴加草酰氯 (1.23 g, 10 mmol), 油浴升温至 30 °C 反应 3 h。降温至室温。反应液无需处理, 直接用于下一步反应。

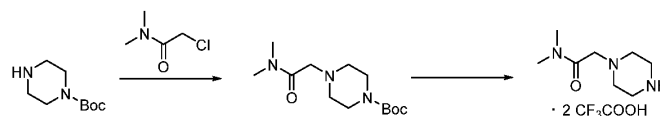
第二、三步: 2-(二甲基氨基)-1-(哌嗪-1-基)乙酮盐酸盐



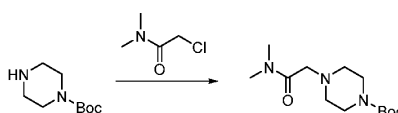
- 10 以 N, N-二甲氨基乙酰氯盐酸盐和哌嗪-1-甲酸叔丁酯为原料, 制备过程参见实施例 33。

实施例 45

N, N-二甲基-2-(哌嗪-1-基)乙酰胺三氟乙酸盐

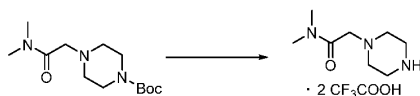


- 15 第一步: 4-(2-(二甲基氨基)-2-氧代乙基)哌嗪-1-甲酸叔丁酯



于 100 mL 单口瓶中依次加入 N, N-二甲基-2-氯乙酰胺 (200 g, 1.65 mmol), THF (10 mL), 三乙胺 (334 mg, 2 eq) 和哌嗪-1-甲酸叔丁酯 (337 mg, 1.1 eq), 室温搅拌反应。TLC 监控反应, 反应完成后, 将反应液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 20/1, 收集产品, 减压浓缩得 410 mg。

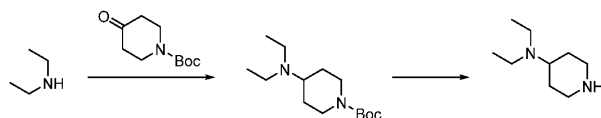
5 第二步: N, N-二甲基-2-(哌嗪-1-基)乙酰胺三氟乙酸盐



于 100 mL 单口瓶中依次加入 4-(2-(二甲基氨基)-2-氧代乙基)哌嗪-1-甲酸叔丁酯, DCM (10 mL) 和三氟乙酸 (2 mL), 室温搅拌反应, TLC 监测反应, 反应完成后, 将反应液减压浓缩干得 600 mg 三氟乙酸盐。

10 实施例 46

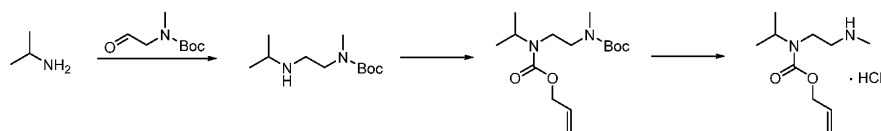
4-(二乙基氨基)哌啶



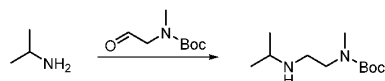
以二乙胺和 N-叔丁氧羰基-4-哌啶酮为原料, 制备过程参见实施例 15。

实施例 47

15 异丙基(2-(甲基氨基)乙基)氨基甲酸烯丙酯盐酸盐

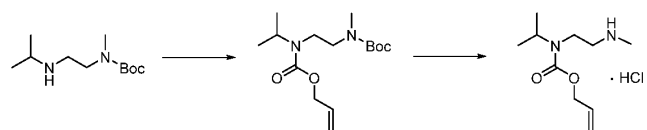


第一步: (2-(异丙基氨基)乙基)(甲基)氨基甲酸叔丁酯



以异丙胺和 N-Boc-(甲胺基)乙醛为原料, 制备过程参见实施例 15 第一步。

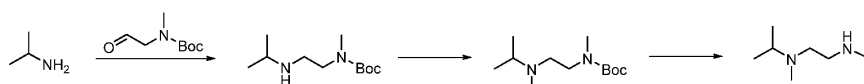
第二、第三步：异丙基（2-（甲基氨基）乙基）氨基甲酸烯丙酯盐酸盐



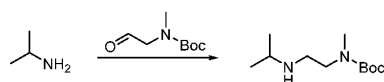
以（2-（异丙基氨基）乙基）（甲基）氨基甲酸叔丁酯和氯甲酸烯丙酯为原料，制备过程参见实施例 33。

5 实施例 48

N1-异丙基-N1, N2-二甲基乙二胺

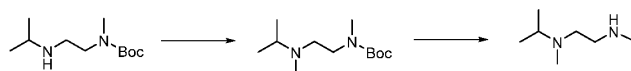


第一步：甲基（2-（异丙基氨基）乙基）氨基甲酸叔丁酯



10 以异丙胺和 N-Boc-（甲胺基）乙醛为原料，制备过程参见实施例 15 第一步。

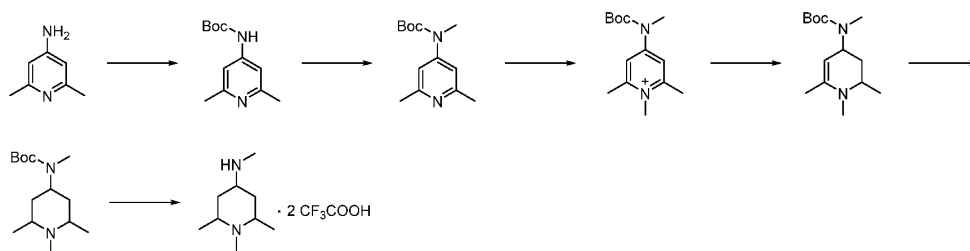
第二、第三步：N1-异丙基-N1, N2-二甲基乙二胺



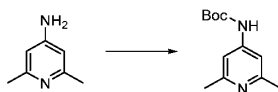
以甲基（2-（异丙基氨基）乙基）氨基甲酸叔丁酯和 CH_3I 为原料，制备过程参见实施例 2 第二、三步。

15 实施例 49

N, 1, 2, 6-四甲基哌啶-4-胺三氟乙酸盐

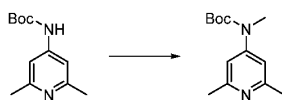


第一步: (2, 6-二甲基吡啶-4-基) 氨基甲酸叔丁酯



于 100 mL 三口瓶中依次加入 2, 6-二甲基吡啶-4-胺 (1 g, 8.2 mmol), DCM (20 mL) 三乙胺 (1.66 g, 16.4 mmol) 和 DMAP (0.1 g, 0.82 mmol), 室温搅拌下滴加 (Boc)₂O (1.79 g, 8.2 mmol) 的 DCM (5 mL) 溶液, 滴完后室温搅拌反应 1-2 h。向反应体系中加入纯化水 (50 mL) 和 DCM (30 mL), 过滤, 滤液静置分层, 水相用 DCM 萃取 2 次, 合并有机相, 饱和食盐水洗 2 次, 无水硫酸钠干燥, 减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 25/1, 收集产品, 减压浓缩得 750 mg 白色固体。

第二步: (2, 6-二甲基吡啶-4-基) (甲基) 氨基甲酸叔丁酯

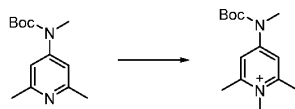


10

氩气保护下, 于 100 mL 三口瓶依次加入 DMF (30 mL) 和 NaH (406 mg, 10.13 mmol), 冰水浴降温至 0-5 °C, 滴加 (2, 6-二甲基吡啶-4-基) 氨基甲酸叔丁酯 (750 mg, 3.38 mmol) 的 DMF (5 mL) 溶液, 滴加完成后 0-5 °C 反应 1 h。滴加 CH₃I (720 mg, 1.5 eq) 的 DMF (5 mL) 溶液, 升温至室温搅拌反应 1-2 h。反应完全后, 降温至 0-10 °C, 滴加纯化水 (15 mL), 乙酸乙酯萃 (20 mL × 3) 取 3 次, 合并有机相, 饱和食盐水洗两次, 无水硫酸钠干燥, 减压浓缩得 900 mg 淡黄色液体。

15

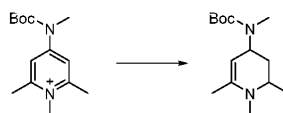
第三步: 4-((叔丁氧基羰基) (甲基) 氨基) -1, 2, 6 三甲基吡啶鎓



于 50 mL 反应釜中依次加入 (2, 6-二甲基吡啶-4-基) (甲基) 氨基甲酸叔丁酯 (400

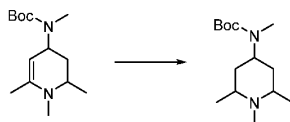
mg, 1.69 mmol), DMF (10 mL) 和 CH_3I (1.2 g, 8.47 mmol), 油浴升温到 75-80 °C, 密闭条件下搅拌反应 7-8 h。降温到室温, 无需处理, 直接用于下一步反应。

第四步: (1, 2, 6-三甲基-1, 2, 3, 4-四氢吡啶-4-基)(甲基)氨基甲酸叔丁酯



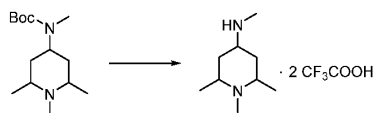
- 5 于 250 mL 三口瓶中依次加入上步反应液, 乙醇 (30 mL) 和水 (3 mL), 冰水浴降温到 0-5 °C, 分批加入 NaBH_4 (241 mg, 6.37 mmol), 升温至室温搅拌反应过夜。向反应体系中加入纯化水 (50 mL), 乙酸乙酯 (50 mL $\times$ 3) 萃取 3 次, 合并有机相, 饱和食盐水洗 2 次, 无水硫酸钠干燥, 减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: $\text{DCM}/\text{MeOH} = 10/1$, 收集产品, 减压浓缩得 110 mg 油状产品。

10 第五步: (1, 2, 6-三甲基哌啶-4-基)(甲基)氨基甲酸叔丁酯



于 100 mL 单口瓶依次加入 (1, 2, 6-三甲基-1, 2, 3, 4-四氢吡啶-4-基)(甲基)氨基甲酸叔丁酯 (110 mg, 0.43 mmol), 甲醇 (10 mL) 和 Pd/C (20 mg), 置换氢气三次, 室温搅拌反应 2-3 h。过滤, 滤液减压浓缩得 115 mg 油状产品。

15 第六步: N, 1, 2, 6-四甲基哌啶-4-胺三氟乙酸盐



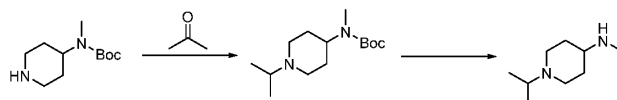
于 100 mL 三口瓶中依次加入 (1, 2, 6-三甲基哌啶-4-基)(甲基)氨基甲酸叔丁酯 (115 mg, 0.45 mmol) 和 DCM (5 mL), 室温搅拌下滴加三氟乙酸 (3 mL), 滴加完毕

后室温搅拌反应。反应完成后，减压浓缩，残留物用乙酸乙酯溶解后继续减压浓缩得 180 mg 剩余物。无需处理，直接用于下一步反应。

实施例 50

1-异丙基-N-甲基哌啶-4-胺

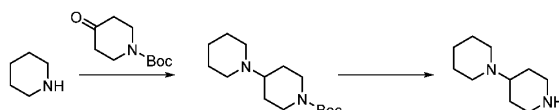
5



以甲基（哌啶-4-基）氨基甲酸叔丁酯和丙酮为原料，制备过程参见实施例 15。

实施例 51

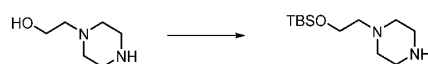
4-哌啶基哌啶



10 以 N-叔丁氧羰基-4-哌啶酮和哌啶为原料，制备过程参见实施例 15。

实施例 52

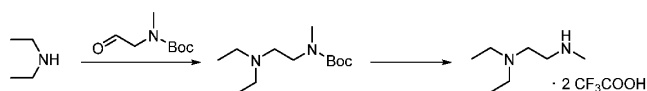
1-(2-((叔丁基二甲基硅烷基)氧基)乙基)哌嗪



以 1-(2-羟乙基)哌嗪为原料，制备过程参见实施例 30 第三步。

15 实施例 53

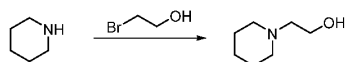
N, N-二乙基-N'-甲基乙二胺三氟乙酸盐



以乙二胺和 N-Boc-（甲胺基）乙醛为原料，制备过程参见实施例 15。

实施例 54

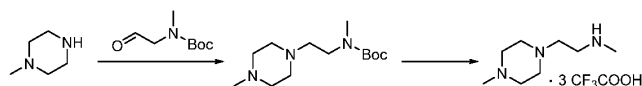
1-羟乙基哌啶



- 于 100 mL 三口瓶加入 2-溴乙醇(1 g)和 DCM(24 mL),磁力搅拌下加入哌啶(2 mL),
室温反应过夜。减压浓缩,往剩余物中加入甲基叔丁基醚(10 mL),搅拌,过滤,滤液
5 减压浓缩得粗品,粗品经柱层析纯化,洗脱液: DCM/MeOH = 10/1,收集产品,减压浓
缩得 570 mg 产品。

实施例 55

N-甲基-2-(4-甲基哌嗪-1-基)乙胺三氟乙酸盐



- 10 以 N-Boc-(甲胺基)乙醛和甲基哌嗪为原料,制备过程参见实施例 15。

实施例 56

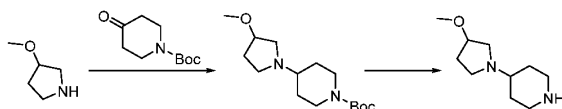
N-异丙基-N,N'-二甲基乙二胺盐酸盐



以 N,N'-二甲基乙二胺为原料,制备过程参见实施例 2。

- 15 实施例 57

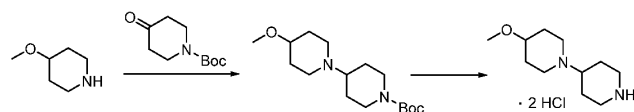
4-(3-甲氧基吡咯烷-1-基)哌啶



以 3-甲氧基吡咯烷和 N-叔丁氧羰基-4-哌啶酮为原料,制备过程参见实施例 15。

实施例 58

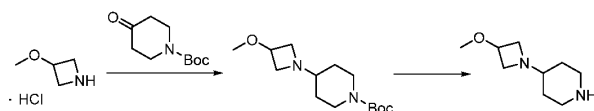
4- (4-甲氧基哌啶-1-基) 哌啶盐酸盐



以 4-甲氧基哌啶和 N-叔丁氧羰基-4-哌啶酮为原料, 制备过程参见实施例 15。

实施例 59

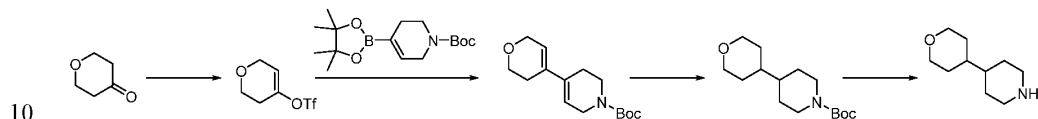
5 4- (3-甲氧基吡啶-1-基) 哌啶



以 3-甲氧基吡啶盐酸盐和 N-叔丁氧羰基-4-哌啶酮为原料, 制备过程参见实施例 15。

实施例 60

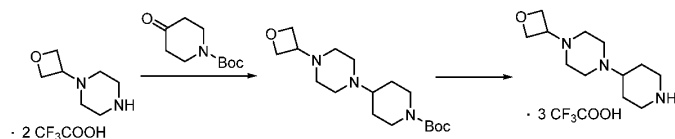
4- (四氢吡喃-4-基) 哌啶



以四氢吡喃酮为原料, 制备过程参见实施例 18。

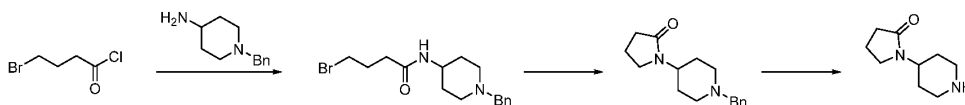
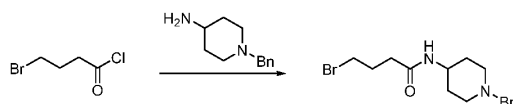
实施例 61

1- (3-氧杂环丁基) -4- (哌啶-4-基) 哌嗪三氟乙酸盐

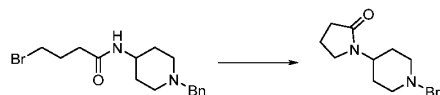


以 1- (3-氧杂环丁基) 哌嗪三氟乙酸盐和 N-叔丁氧羰基-4-哌啶酮为原料, 制备过程参见实施例 15。

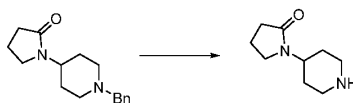
实施例 62

1-(哌啶-4-基)吡咯烷-2-酮**第一步: N-(1-苄基哌啶-4-基)-4-溴丁酰胺**

- 5 于 100 mL 三口瓶中依次加入 1-苄基哌啶-4-胺 (2.5 g, 1.0 eq), DCM (30 mL) 和吡啶 (1.5 eq), 降温至 0 °C, 然后滴加 4-溴丁酰氯 (1.2 eq), 0 °C 反应, TLC 监控反应进程。反应结束后, 加入饱和的碳酸钾溶液 (30 mL), DCM (30 mL × 2) 萃取 2 次, 合并有机相, 无水硫酸钠干燥, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 梯度洗脱, 洗脱液: DCM/MeOH = 80/1 → 25/1, 收集产品, 减压浓缩得 4 g 油状物。

第二步: 1-(1-苄基哌啶-4-基)吡咯烷-2-酮

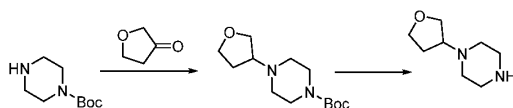
- 10 100 mL 单口瓶中加入 N-(1-苄基哌啶-4-基)-4-溴丁酰胺 (4 g, 1.0 eq) 和 THF (30 mL), 降温到 0 °C, 然后将钠氢 (2.0 eq) 分批加入上述体系, 保持室温反应, TLC 监测反应, 加入饱和的碳酸钾溶液 (30 mL), DCM (30 mL × 2) 萃取 2 次, 合并有机相, 饱和食盐水洗 2 次, 有机相用无水硫酸钠干燥, 过滤, 母液减压浓缩干得粗品, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 100/1 → 25/1 冲下产品点, 减压浓缩干得 1.6 g 油状物。

第三步: 1-(哌啶-4-基)吡咯烷-2-酮

于 100 mL 单口瓶中加入 1-(1-苄基哌啶-4-基)吡咯烷-2-酮 (1.6 g, 1.0 eq) 和甲醇 (30 mL), 搅拌溶解后加入 10% Pd/C 和甲酸铵 (6.5 eq), 加热回流反应, TLC 监测反应进程, 过滤, 滤液减压浓缩得 1.1 g 油状物直接用于下一步。

实施例 63

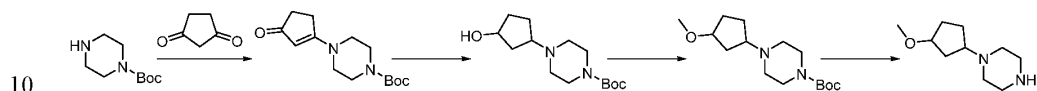
5 1-(四氢呋喃-3-基)哌嗪



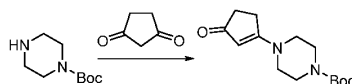
以二氢-3(2H)-呋喃酮和哌嗪-1-甲酸叔丁酯为原料, 制备过程参见实施例 15。

实施例 64

1-(3-甲氧基环戊基)哌嗪

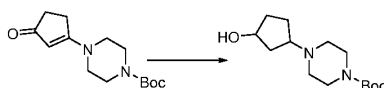


第一步: 4-(3-氧代环戊-1-烯-1-基)哌嗪-1-甲酸叔丁酯



于 250 mL 单口瓶中依次加入 1, 3-环戊二酮 (7 g, 38 mmol), 哌嗪-1-甲酸叔丁酯 (7.4 g, 75 mmol) 和 DCM (100 mL), 室温搅拌 24 h。反应液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: DCM/MeOH = 10/1, 收集产品, 减压浓缩得 12 g 白色固体。

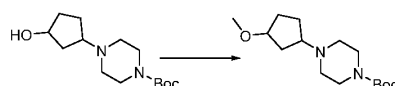
第二步: 4-(3-羟基环戊基)哌嗪-1-甲酸叔丁酯



于 1 L 三口瓶中加入氢化铝锂 (6.8 g, 180 mmol) 和四氢呋喃 (200 mL), 冰盐浴降温-5-0 °C, 滴加 4-(3-氧代环戊-1-烯-1-基)哌嗪-1-甲酸叔丁酯 (12 g, 45 mmol) 的四

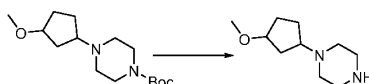
氢呋喃(200 mL)溶液, 0 °C反应 30 min。冰盐浴-5-0 °C下向反应液中缓慢滴加水, DCM (50 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水(100 mL × 3) 洗 3 次, 无水硫酸钠干燥 30 min, 减压抽滤, 滤液 45 °C减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: DCM/MeOH = 10/1, 收集产品, 减压浓缩得 1.76 g 红棕色固体。

5 第三步: 4-(3-甲氧基环戊基)哌嗪-1-甲酸叔丁酯



于 100 mL 单口瓶中加入 4-(3-羟基环戊基)哌嗪-1-甲酸叔丁酯(1.73 g, 6.4 mmol) 和 DMF(50 mL), 搅拌溶解, 冰盐浴降温至-5-0 °C, 分批加叔丁醇钠(1.23 g, 12.8 mmol), 保温反应 30 min。加入水(30 mL), 乙酸乙酯(30 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水(20 mL × 3) 洗 3 次, 无水硫酸钠干燥 30 min, 减压抽滤, 滤液 45 °C减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: DCM/MeOH = 50/1, 收集产品, 减压浓缩得 1.25 g 黄色油状物。

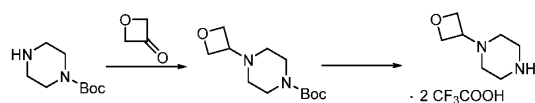
第四步: 1-(3-甲氧基环戊基)哌嗪



于 100 mL 单口瓶中加入 4-(3-甲氧基环戊基)哌嗪-1-甲酸叔丁酯(1.25 g, 4.4 mmol) 和 DCM(20 mL), 搅拌溶解, 滴加三氟乙酸(10 g, 88 mmol), 室温反应 2 h。反应液于 50 °C减压浓缩, 向剩余物中加入无水乙醇(10 mL), 50 °C减压浓缩, 向剩余物中加异丙醚, 室温磁力搅拌 1 h, 析出白色固体, 过滤, 滤饼于 50 °C鼓风干燥得 1.6 g 白色固体。

20 实施例 65

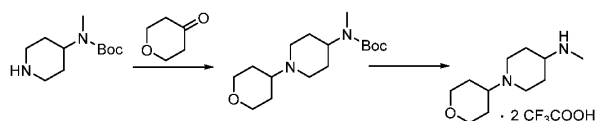
1-(3-氧杂环丁基)哌嗪三氟乙酸盐



以 3-氧杂环丁酮和 1-Boc-哌嗪为原料, 制备过程参见实施例 15。

实施例 66

N-甲基-1-(四氢-2H-吡喃-4-基)哌啶-4-胺三氟乙酸盐

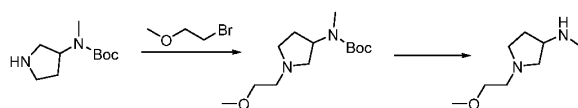


5

以 4-N-叔丁氧羰基-4-N-甲基氨基哌啶和四氢吡喃酮为原料, 制备过程参见实施例 15。

实施例 67

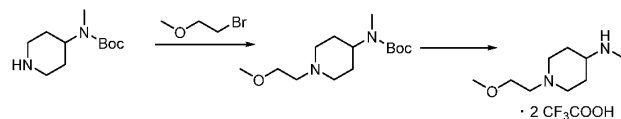
1-(2-甲氧基乙基)-N-甲基吡咯烷-3-胺



10 以 3-N-Boc-N-甲基氨基吡咯烷和 2-溴乙基甲基醚为原料, 制备过程参见实施例 45。

实施例 68

1-(2-甲氧基乙基)-N-甲基哌啶-4-胺三氟乙酸盐

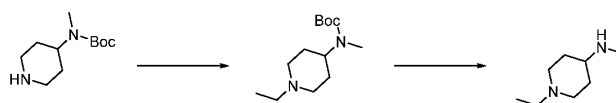


以 4-N-叔丁氧羰基-4-N-甲基氨基哌啶和 2-溴乙基甲基醚为原料, 制备过程参见实施

15 例 45。

实施例 69

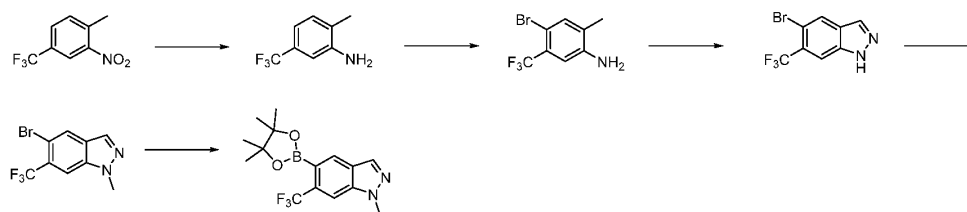
1-N-乙基-N-甲基哌啶-4-胺



以 4-N-叔丁氧羰基-4-N-甲基氨基哌啶和碘乙烷为原料，制备过程参见实施例 1。

实施例 70

1-甲基-6-(三氟甲基)吡唑-5-硼酸频哪醇酯的制备



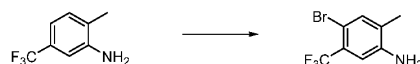
5

第一步：2-甲基-5-(三氟甲基)苯胺



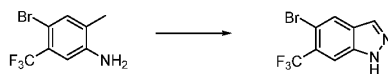
向 100 mL 单口瓶中依次加入 1-甲基-2-硝基-4-(三氟甲基)苯 (3 g, 14 mmol)，乙醇 (30 mL)，Pd/C (100 mg)。室温加氢反应 12-14 h，反应液过滤，滤液减压浓缩，得到 2.6 g 淡黄色油状物，收率：101.5%。

第二步：4-溴-2-甲基-5-(三氟甲基)苯胺



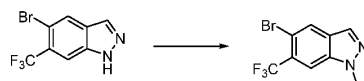
向 100 mL 单口瓶中依次加入 2-甲基-5-(三氟甲基)苯胺 (2.6 g, 14 mmol) 和乙腈 (40 mL)，降温至 10 °C，分批加入 NBS (2.9 g, 16 mmol)。加毕，25 °C 反应 1.5 h。加入 50 mL 饱和硫代硫酸钠水溶液淬灭反应，水相用乙酸乙酯 (80 mL × 3) 萃取 3 次，合并有机相，减压浓缩，得到粗品。粗品经柱层析纯化，用 PE/EA = 6/1 洗脱，收集产品并浓缩，得 3.43 g 淡黄色油状物，收率：91.5%。

第三步: 5-溴-6-(三氟甲基)-1H-吲唑



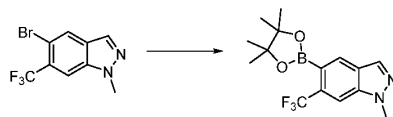
向 100 mL 单口瓶中依次加入 4-溴-2-甲基-5-(三氟甲基)苯胺 (3.43 g, 13.55 mmol) 和乙酸 (130 mL), 滴加亚硝酸钠 (1.02 g, 14.91 mmol) 的水溶液 (3.5 mL)。加毕, 室温反应 12-14 h。向反应液中加入饱和碳酸钠水溶液 (PH>7), 过滤, 收集滤饼, 用 30 mL 石油醚打浆 20 min, 过滤, 烘干, 得 2.2 g 淡黄色固体, 收率: 61.6%。

第四步: 5-溴-1-甲基-6-(三氟甲基)-1H-吲唑



向 100 mL 三口瓶中依次加入 5-溴-6-(三氟甲基)-1H-吲唑 (2.2 g, 8.33 mmol), 四氢呋喃 (20 mL), 降温至 0 °C, 加入氢化钠 (433 mg, 10.83 mmol)。加毕, 保温 0 °C 搅拌反应 30 min。控制温度在 0 °C, 滴加碘甲烷 (1.77 g, 12.5 mmol) 的 THF(4 mL) 溶液, 滴毕, 升温至室温搅拌反应 2 h。加入 20 mL 水淬灭反应, 水相用乙酸乙酯 (60 mL × 3) 萃取 3 次, 合并有机相, 减压浓缩, 得到粗品。粗品经柱层析纯化, 以 PE/EA = 10/1 洗脱, 收集产品并浓缩, 得 600 mg 淡黄色固体, 收率: 26.1%。

第五步: 1-甲基-6-(三氟甲基)吲唑-5-硼酸频哪醇酯

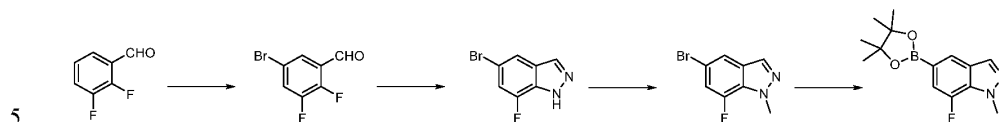


氩气保护下, 向 100 mL 单口瓶中依次加入 5-溴-1-甲基-6-(三氟甲基)-1H-吲唑 (500 mg, 1.79 mmol), 双联频哪醇硼酸酯 (685.2 mg, 2.69 mmol), 乙酸钾 (352.5 mg, 3.58 mmol), Pd(dppf)Cl₂ (131.6 mg, 0.179 mmol) 和二氧六环 (15 mL), 加毕, 升温至 100 °C 反应 7 h。反应体系降温至室温, 向反应液中加入 20 mL 水, 水相用乙酸乙酯 (50 mL × 3) 萃

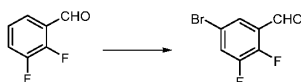
取 3 次, 合并有机相, 浓缩, 得到粗品。粗品经柱层析纯化, 用 PE/EA = 10/1 洗脱, 收集产品并浓缩, 得 300 mg 淡黄色油状物, 收率: 51.1%。

实施例 71

1-甲基-7-氟吡唑-5-硼酸频哪醇酯的制备

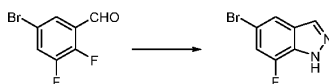


第一步: 5-溴-2,3-二氟苯甲醛



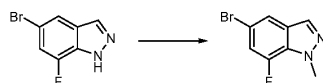
于 100 mL 三口瓶中依次加入 2,3-二氟苯甲醛 (1 g, 7.04 mmol) 和浓硫酸 (50 mL), 室温搅拌溶解, 得棕黄色反应液。分批缓慢加入 NBS (1.05 g, 5.90 mmol), 加毕, 升温
10 到 45-50 °C 反应 2-3 h。将反应液缓慢滴加入 200 mL 冰水中, 用乙酸乙酯 (50 mL × 2) 萃取 2 次, 合并有机相, 用饱和食盐水洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 得 280 mg。原料回收。

第二步: 5-溴-7-氟-1H-吡唑



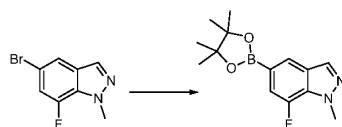
15 于 100 mL 三口瓶中依次加入 5-溴-2,3-二氟苯甲醛 (200 mg) 和水合肼 (10 mL), 升温到 100-110 °C, 搅拌反应 3-4 h, 降温到室温, 加入 30 mL 纯化水, 30 mL 乙酸乙酯, 搅拌分液, 水相用乙酸乙酯 (20 mL × 3) 萃取 3 次, 合并有机相, 用饱和食盐水 (30 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 用 PE/EA = 4/1 洗脱, 收集产品并浓缩得 32 mg。

20 第三步: 1-甲基-5-溴-7-氟-1H-吡唑



以 5-溴-7-氟-1H-吡唑为原料，制备过程参见实施例 70 第四步。

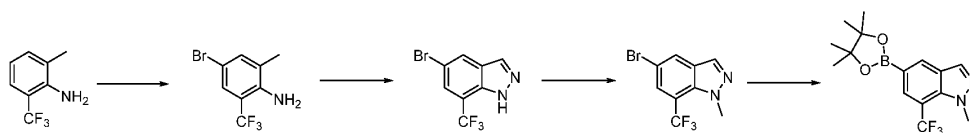
第四步：1-甲基-7-氟吡唑-5-硼酸频哪醇酯



5 以 1-甲基-5-溴-7-氟-1H-吡唑为原料，制备过程参见实施例 70 第五步。

实施例 72

1-甲基-7-(三氟甲基)吡唑-5-硼酸频哪醇酯的制备

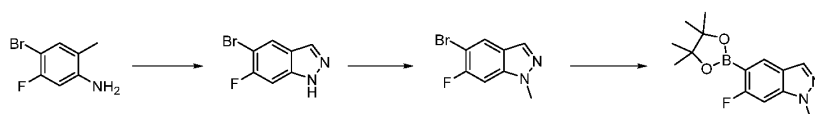


以 2-甲基-6-(三氟甲基)苯胺为起始原料，制备过程参见实施例 70 第二、三、四、

10 五步。

实施例 73

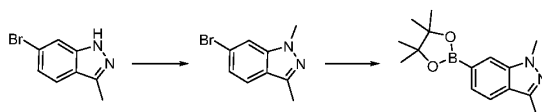
1-甲基-6-氟吡唑-5-硼酸频哪醇酯的制备



以 4-溴-5-氟-2-甲基苯胺为原料，制备过程参见实施例 70 第三、四、五步。

15 实施例 74

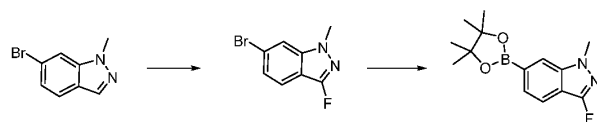
1,3-二甲基吡唑-6-硼酸频哪醇酯的制备



以 6-溴-3-甲基-1H-吡唑为原料，制备过程参见实施例 70 第四、五步。

实施例 75

1-甲基-3-氟吡唑-6-硼酸频哪醇酯的制备

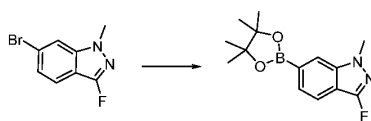


5 第一步：1-甲基-6-溴-3-氟-1H-吡唑



- 于 100 mL 单口瓶中依次加入 6-溴-1-甲基-1H-吡唑 (2 g, 9.48 mmol), selectfluor (氟试剂) (4.4 g, 12.32 mmol) 和乙腈 (40 mL), 油浴升温至 100 °C 搅拌反应。TLC 监测反应。反应完毕后, 降温至室温, 加入纯化水 (60 mL), 乙酸乙酯 (80 mL), 萃取分液,
- 10 有机相用饱和食盐水 (50 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min。过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 用 PE/EA = 10/1 洗脱, 收集产品并减压浓缩得白色固体 620 mg。

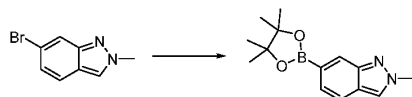
第二步：1-甲基-3-氟吡唑-6-硼酸频哪醇酯



- 15 以 1-甲基-6-溴-3-氟-1H-吡唑为原料, 制备过程参见实施例 70 第五步。

实施例 76

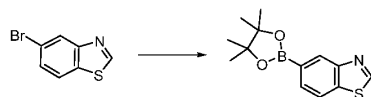
2-甲基-2H-吡唑-6-硼酸频哪醇酯的制备



以 6-溴-2-甲基-2H-吡唑为原料, 制备过程参见实施例 70 第五步。

实施例 77

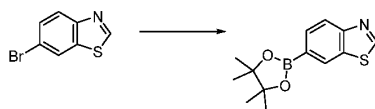
苯并噻唑-5-硼酸频哪醇酯的制备



以 5-溴苯并噻唑为原料，DMF 为溶剂，制备过程参见实施例 70 第五步。

5 实施例 78

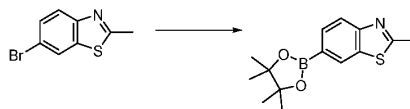
苯并噻唑-6-硼酸频哪醇酯的制备



以 6-溴苯并噻唑为原料，DMF 为溶剂，制备过程参见实施例 70 第五步。

实施例 79

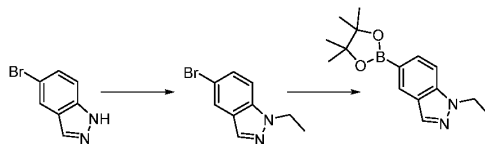
10 2-甲基-苯并噻唑-6-硼酸频哪醇酯的制备



以 6-溴-2-甲基苯并噻唑为原料，制备过程参见实施例 70 第五步。

实施例 80

1-乙基吡唑-5-硼酸频哪醇酯的制备

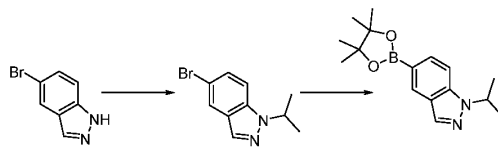


15

以 5-溴吡唑和 C_2H_5I 为原料，制备过程参见实施例 70 第四、五步。

实施例 81

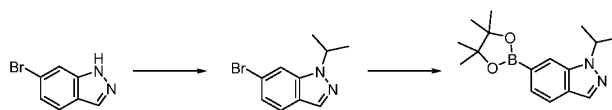
1-异丙基吡唑-5-硼酸频哪醇酯的制备



以 5-溴吲唑和碘代异丙烷为原料，制备过程参见实施例 70 第四、五步

实施例 82

1-异丙基吲唑-6-硼酸频哪醇酯的制备

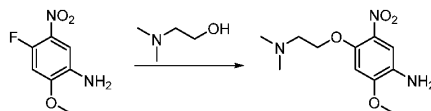


5

以 6-溴吲唑和碘代异丙烷为原料，制备过程参见实施例 70 第四、五步

实施例 83

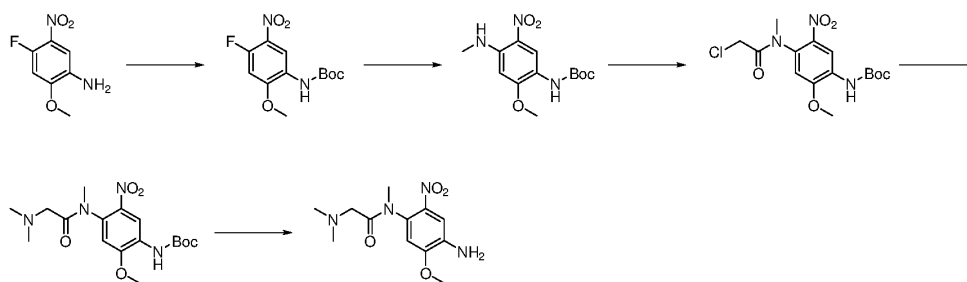
4-(2-(二甲基氨基)乙氧基)-2-甲氧基-5-硝基苯胺



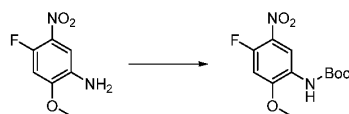
- 10 于 100 mL 三口瓶中加入 2-(二甲基氨基)乙醇 (718 mg, 8.06 mmol) 和 DMF (30 mL), 冰水浴降温至 0-5 °C, 分批加入叔丁醇钾 (1.5 g, 13.4 mmol), 保温反应 30 min, 然后加入 4-氟-2-甲氧基-5-硝基苯胺 (500 mg, 2.69 mmol), 保温反应 20 min。TLC 监控反应至原料反应完全, 降温至室温。加入水 (50 mL), 用乙酸乙酯萃 (50 mL × 3) 取 3 次, 合并有机相, 饱和食盐水 (20 mL × 3) 洗 3 次, 无水硫酸钠干燥 30 min, 减压抽滤,
- 15 滤液于 45 °C 减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: DCM/MeOH = 10/1, 收集产品, 减压浓缩得 265 mg 棕色油状物。

实施例 84

N-(4-氨基-5-甲氧基-2-硝基苯基)-2-(二甲基氨基)-N-甲基乙酰胺

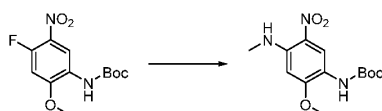


第一步: (4-氟-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯



向 250 mL 单口瓶中依次加入 4-氟-2-甲氧基-5-硝基苯胺 (5 g, 27 mmol), 4-二甲氨基吡啶 (0.33 g, 2.7 mmol) 和 DCM (50 mL), 搅拌 10 min, 然后加入三乙胺 (5.4 g, 53.75 mmol) 和 $(\text{Boc})_2\text{O}$ (5.87 g, 27 mmol), 滴毕, 室温反应 4.5 h。加入水 (30 mL), 用 DCM 萃取 3 次 ($40\text{ mL} \times 3$), 合并有机相, 饱和食盐水洗 3 次 ($20\text{ mL} \times 3$), 无水硫酸钠干燥 30 min, 减压抽滤, 滤液于 $45\text{ }^\circ\text{C}$ 减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: PE/EA = 10/1, 收集产品, 减压浓缩得 5.34 g 棕黄色固体。

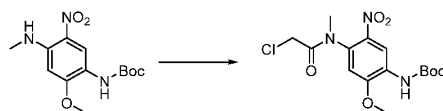
10 第二步: (2-甲氧基-4-(甲基氨基)-5-硝基苯基)氨基甲酸叔丁酯



向 100 mL 反应釜中依次加入 (4-氟-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯 (1.7 g, 5.9 mmol), 甲胺盐酸盐 (1.2 g, 17.8 mmol), 碳酸钠 (3.15 g, 29.7 mmol), 碘化钾 (986 mg, 5.9 mmol) 和 N-甲基吡咯烷酮 (30 mL), 油浴升温至 $60\text{ }^\circ\text{C}$ 反应 7 h。降温至室温, 加入水 (30 mL), 用乙酸乙酯 ($20\text{ mL} \times 3$) 萃取 3 次, 合并有机相, 饱和食盐水 ($20\text{ mL} \times 3$) 洗 3 次, 无水硫酸钠干燥 0.5 h, 减压抽滤, 滤液于 $45\text{ }^\circ\text{C}$ 减压浓缩得 1.9 g 红棕色

固体粗品。

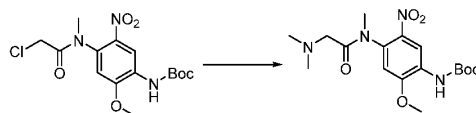
第三步: (4-(2-氯-N-甲基乙酰氨基)-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯



氮气保护下, 向 100 mL 的三口瓶中依次加 (2-甲氧基-4-(甲基氨基)-5-硝基苯基)

- 5 氨基甲酸叔丁酯 (1.7 g, 6 mmol), 碳酸钾 (4 g, 28.6 mmol), 30 mL 四氢呋喃和氯乙酰氯 (1.9 g, 17 mmol), 油浴升温至 70 °C 反应 3 h。向反应液中加入水 (30 mL), 乙酸乙酯 (30 mL × 3) 萃取 3 次, 饱和食盐水 (20 mL × 3) 洗 3 次, 无水硫酸钠干燥 0.5 h, 减压抽滤, 滤液于 45 °C 减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: PE/EA = 1/1, 收集产品, 减压浓缩得 1.5 g 淡黄色固体。

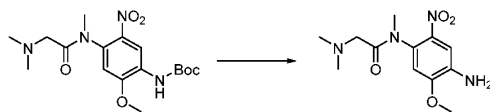
- 10 **第四步: (4-(2-(二甲基氨基)-N-甲基乙酰氨基)-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯**



向 100 mL 的反应釜中依次加 (4-(2-氯-N-甲基乙酰氨基)-2-甲氧基-5-硝基苯基)

- 氨基甲酸叔丁酯 (1.5 g, 4 mmol), 二甲胺盐酸盐 (982 mg, 12 mmol), 碳酸钾 (2.8 g, 20 mmol) 和丙酮 (30 mL), 油浴升温至 50 °C 反应 15 h。向反应液中加入水 (30 mL), 乙酸乙酯 (30 mL × 3) 萃取 3 次, 饱和食盐水 (20 mL × 3) 洗 3 次, 无水硫酸钠干燥 0.5 h, 减压抽滤, 滤液于 45 °C 减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: DCM/MeOH = 10/1, 收集产品, 减压浓缩得 1.2 g 红棕色油状物。

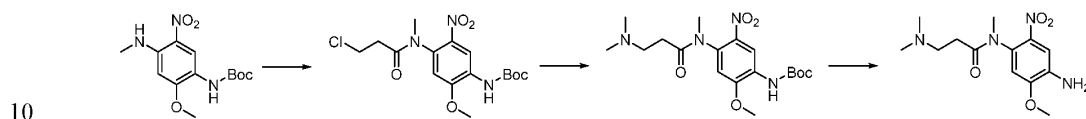
第五步: N-(4-氨基-5-甲氧基-2-硝基苯基)-2-(二甲基氨基)-N-甲基乙酰胺



向 100 mL 的单口瓶中加入 (4-(2-(二甲基氨基)-N-甲基乙酰氨基)-2-甲氧基-5-硝基苯基) 氨基甲酸叔丁酯 (1.2 g, 3.1 mmol) 和 DCM (20 mL), 搅拌溶解, 然后滴加三氟乙酸 (7.2 g, 62.8 mmol), 室温反应 2.5 h。向反应液中加入水 (30 mL), 分批加碳酸钠固体调 pH>8, 乙酸乙酯 (30 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水 (20 mL × 3) 洗 3 次, 无水硫酸钠干燥 0.5 h, 减压抽滤, 滤液于 45 °C 减压浓缩得 673 mg 黄色固体。

实施例 85

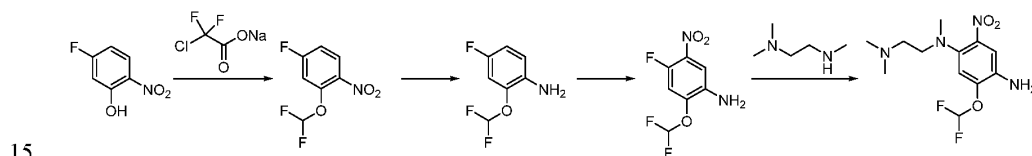
N-(4-氨基-5-甲氧基-2-硝基苯基)-2-(二甲基氨基)-N-甲基丙酰胺



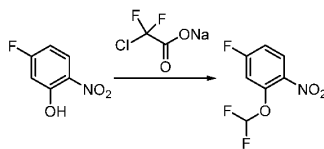
以 (2-甲氧基-4-(甲基氨基)-5-硝基苯基) 氨基甲酸叔丁酯和氯丙酰氯为原料, 制备过程参见实施例 84。

实施例 86

5-(二氟甲氧基)-N1-(2-(二甲基氨基)乙基)-N1-甲基-2-硝基苯-1, 4-二胺

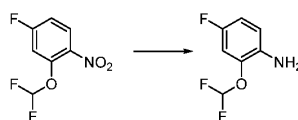


第一步: 4-氟-2-二氟甲氧基硝基苯



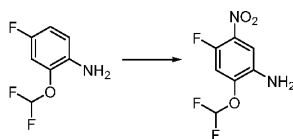
- 氮气保护下, 向 100 mL 单口瓶中依次加入 5-氟-2-硝基苯酚 (3 g, 19.1 mmol), 二氟乙酸钠 (3.8 g, 28.6 mmol), 碳酸钾 (5.28 g, 38.2 mmol) 和 DMF (100 mL), 升温至 80 °C 反应 7-8 h。降温至室温, 加入冰水, 水相用乙酸乙酯 (80 mL × 3) 萃取 3 次, 5 合并有机相, 减压浓缩。粗品经柱层析纯化, 洗脱剂: PE/EA = 20/1, 收集产品, 减压浓缩得 3.26 g 淡黄色油状物, 收率: 82.5%。

第二步: 2-(二氟甲氧基)-4-氟苯胺



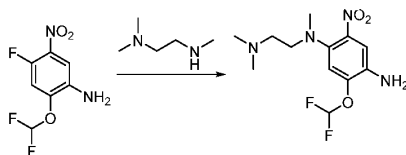
- 向 100 mL 单口瓶中依次加入 4-氟-2-二氟甲氧基硝基苯 (3.26 g, 15.7 mmol), Pd/C (800 mg, 20%) 和甲醇 (50 mL), 置换氢气 2 次, 室温加氢反应 2-3 h。过滤, 滤液减压浓缩得 2.6 g 无色油状物, 收率: 93.5%。

第三步: 2-(二氟甲氧基)-4-氟-5-硝基苯胺



- 向 100 mL 三口瓶中加入浓硫酸 (15 mL), 降温至 0 °C, 加入 2-(二氟甲氧基)-4-氟苯胺 (2.56 g, 14.4 mmol), 0 °C 反应 15 min, 然后分批加入硝酸钾 (1.60 g, 15.9 mmol), 0 °C 反应 2-3 h。将反应液缓慢倒入冰的碳酸钠水溶液中调 pH > 7, 水相用乙酸乙酯 (80 mL × 2) 萃取 2 次, 合并有机相, 减压浓缩得粗品。粗品经柱层析纯化, 洗脱剂: PE/EA = 10/1, 收集产品, 减压浓缩得 1.8 g 淡黄色固体, 收率: 56.3%。

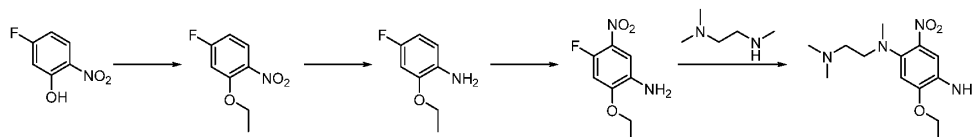
第四步: 5-(二氟甲氧基)-N1-(2-(二甲基氨基)乙基)-N1-甲基-2-硝基苯-1,4-二胺



氩气保护下,向 100 mL 单口瓶中依次加入 2-(二氟甲氧基)-4-氟-5-硝基苯胺(1 g, 4.5 mmol), N1, N1, N2-三甲基乙二胺(2.3 g, 22.5 mmol), DIPEA(2.9 g, 22.5 mmol) 和 NMP(20 mL)。升温至 100 °C 反应 4-5 h。降温至室温,向反应体系中加入水(100 mL), 水相用乙酸乙酯(80 mL × 3)萃取 3 次,合并有机相,减压浓缩得粗品。粗品经柱层析(中性 Al₂O₃)纯化,洗脱剂: DCM/MeOH = 50/1,收集产品,减压浓缩得 1.2 g 淡红色油状物,收率: 88.2%。

实施例 87

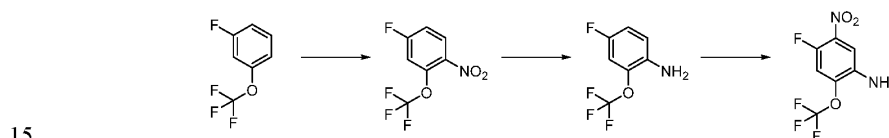
10 5-(乙氧基)-N1-(2-(二甲基氨基)乙基)-N1-甲基-2-硝基苯-1,4-二胺



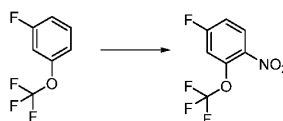
以 5-氟-2-硝基苯酚和 C₂H₅I 为原料,制备过程参见实施例 86。

实施例 88

4-氟-5-硝基-2-(三氟甲氧基)苯胺

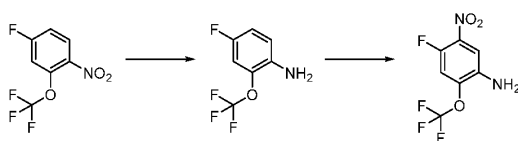


第一步: 4-氟-2-(三氟甲氧基)硝基苯



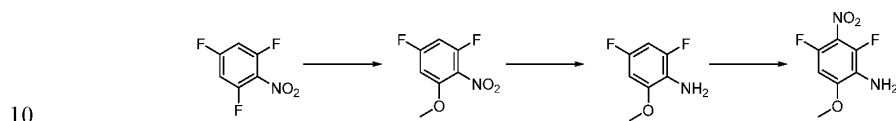
向 250 mL 三口瓶中加入 20 mL 浓硫酸, 冰盐浴降温至 $-5-0^{\circ}\text{C}$, 加入间氟三氟甲氧基苯 (10 g, 60 mmol), 然后分批加入硝酸钾 (5.9 g, 60 mmol), 0°C 搅拌反应 1 h。将反应液缓慢倒入冰水中, 用乙酸乙酯 ($40\text{ mL} \times 3$) 萃取 3 次, 合并有机相, 用饱和食盐水 ($20\text{ mL} \times 3$) 洗 3 次, 无水硫酸钠干燥 0.5 h, 减压抽滤, 滤液于 45°C 减压浓缩得 8.5 g 淡黄色油状物。

第二、三步: 4-氟-5-硝基-2-(三氟甲氧基)苯胺

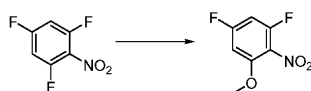


以 4-氟-2-(三氟甲氧基)硝基苯为原料, 制备过程参见实施例 86 第二、三步。

实施例 89



第一步: 1,5-二氟-3-甲氧基-2-硝基苯

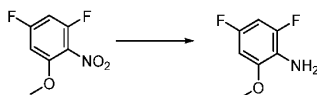


于 100 mL 单口瓶中加入 60 mL 甲醇, 冰水浴降温到 $0-10^{\circ}\text{C}$, 分批加入金属钠 (2.6 g, 112.94 mmol), 搅拌溶解, 得 2N 甲醇钠的甲醇溶液, 氩气保存备用。

于另一干燥 250 mL 三口瓶中依次加入 1,3,5-三氟-2-硝基苯 (10 g, 56.47 mmol) 和甲醇 (100 mL), 搅拌溶解, 降温到 $0-5^{\circ}\text{C}$ 。将上述制备的甲醇钠甲醇溶液滴加入体系, 加毕, 保温反应 2-3 h。滴加入 2N HCl 水溶液调 pH 到中性, 将反应液倒入 200 mL 纯化水中, 用乙酸乙酯 ($100\text{ mL} \times 3$) 萃取三次, 合并有机相, 饱和食盐水 ($100\text{ mL} \times 2$) 洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得 10 g 粗品, 粗品用石油醚 (30 mL)

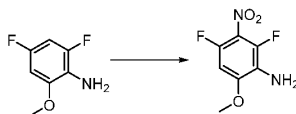
室温搅拌打浆，过滤，滤液减压浓缩得 4 g 油状产品，经柱层析纯化，以 PE/EA = 10/1 洗脱，收集产品减压浓缩得 2.2 g 产品。

第二步：2, 4-二氟-6-甲氧基苯胺



5 于 250 mL 单口瓶中依次加入 1, 5-二氟-3-甲氧基-2-硝基苯 (4.3 g, 1 eq), 甲醇 (50 mL), 乙酸铵 (3.5 g, 2 eq) 和 Pd/C (430 mg, 0.1 eq), 置换氢气 3 次, 室温搅拌反应, TLC 监测反应, 反应结束后过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: PE/EA = 20/1, 收集产品, 减压浓缩得 3.8 g 产物。

第三步：2, 4-二氟-6-甲氧基-3-硝基苯胺

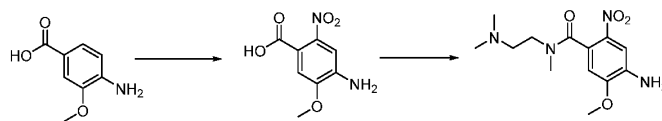


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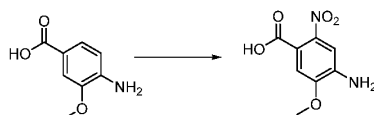
向 100 mL 三口瓶中加入浓硫酸 (20 mL), 冰盐浴降温至 0 °C 左右, 加入 2, 4-二氟-6-甲氧基苯胺 (3.8 g, 1 eq), 搅拌溶解, 然后分批加入硝酸钾 (2.42 g, 1 eq), 保温反应。TLC 监控反应进程。反应结束后将反应液倒入冰水中, 用碳酸钠固体调 pH>7, 乙酸乙酯 (100 mL × 2) 萃取 2 次, 合并有机相, 饱和食盐水 (100 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: PE/EA = 10/1, 收集产品, 减压浓缩得 2.1 g 产物。

实施例 90

4-氨基-N-(2-(二甲基氨基)乙基)-5-甲氧基-N-甲基-2-硝基苯甲酰胺

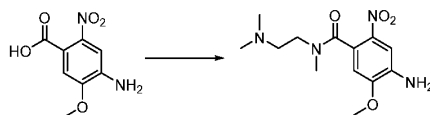


第一步：4-氨基-5-甲氧基-2-硝基苯甲酸



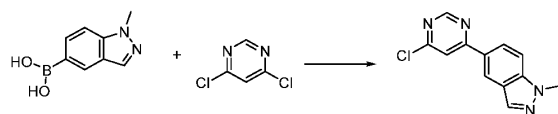
- 于 100 mL 三口瓶加入浓硫酸 (10 mL)，冰盐浴降温至 0 °C，分批加入 4-氨基-3-甲
- 5 氧基苯甲酸 (1.1 g, 6.58 mmol)，加完后保温搅拌 30 min。然后分批加入硝酸钾 (700 mg, 1.05 eq)，保温反应，TLC 监控反应进程。反应结束后，将反应液倒入冰水 (500 mL)，用碳酸钠固体调 pH=3-4 之间，用乙酸乙酯 (300 mL × 3) 萃取 3 次，合并有机相，饱和食盐水 (500 mL × 2) 洗 2 次，无水硫酸钠干燥 30 min，过滤，滤液减压浓缩，向剩余物中加入 DCM (30 mL) 打浆，过滤，滤饼干燥得 1.1 g 固体。

10 第二步：4-氨基-N-(2-(二甲基氨基)乙基)-5-甲氧基-N-甲基-2-硝基苯甲酰胺



- 向 100 mL 单口瓶中依次加入 4-氨基-5-甲氧基-2-硝基苯甲酸 (400 mg, 1.89 mmol)，DMF (20 mL)，EDCI (543 mg, 1.5 eq)，HOBt (384 mg, 1.5 eq)，三乙胺 (574 mg, 3 eq) 和 N1, N1, N2-三甲基乙二胺 (386 mg, 2 eq)，油浴升温到 50-55 °C 搅拌反应。TLC
- 15 监控反应进程，反应结束后，自然降温到室温，加入水 (100 mL)，用乙酸乙酯 (50 mL × 4) 萃取 4 次，合并有机相后，用饱和食盐水 (50 mL × 2) 洗 2 次，无水硫酸钠干燥 30 min，过滤，滤液减压浓缩干得粗品，粗品经柱层析纯化，洗脱液：DCM/MeOH = 10/1，收集产品，减压浓缩得 370 mg 产物。

实施例 91. 中间体 A1 制备



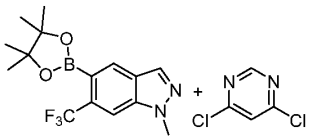
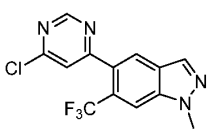
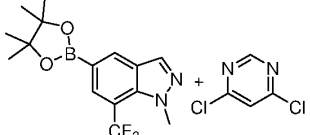
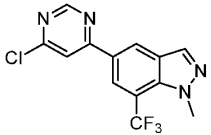
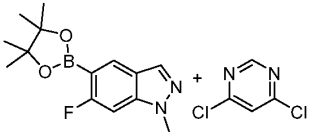
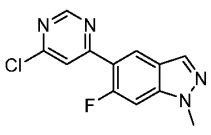
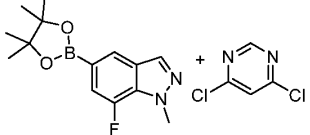
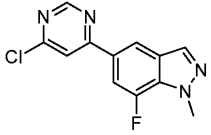
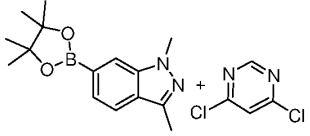
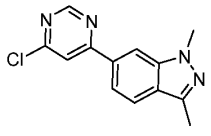
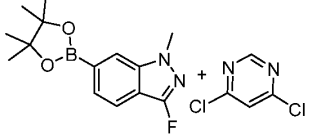
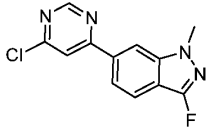
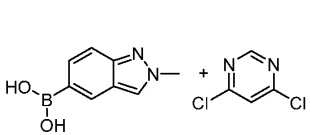
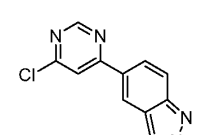
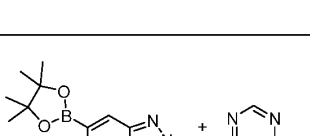
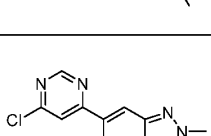
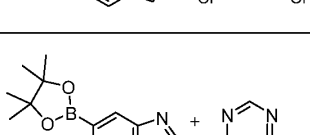
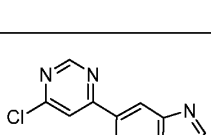
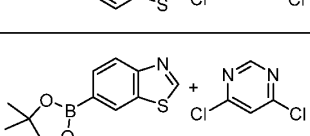
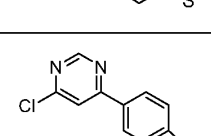
于 100 mL 三口瓶中依次加入 1-甲基吲唑-5-硼酸 (300 mg, 1.70 mmol), 4,6-二氯嘧啶 (330 mg, 2.216 mmol), 碳酸钠 (360 mg, 3.41 mmol) 和乙腈/水 = 4/1 (15 mL)。氮气保护下, 加入四 (三苯基磷) 钯 (200 mg, 0.171 mmol), 油浴升温至 65-70 °C 反应约 7 h, 自然降温至室温。加入水 (50 mL), 二氯甲烷 (50 mL), 搅拌 5 min, 分液, 水相用二氯甲烷 (30 mL × 2) 萃取 2 次。合并有机相, 有机相用饱和食盐水 (50 mL × 2) 洗 2 次, 无水硫酸钠干燥半小时。过滤, 滤液减压浓缩得粗品, 经柱层析纯化, 用 PE/EA = 6/1 洗脱。收集产品并减压浓缩得中间体 A1: 330 mg。

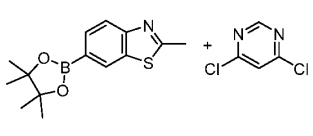
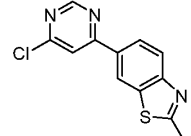
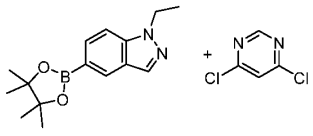
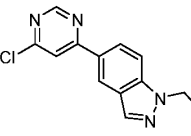
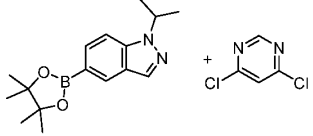
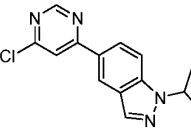
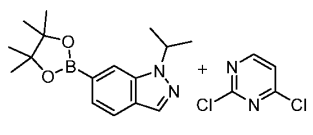
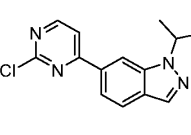
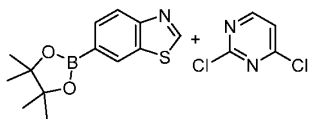
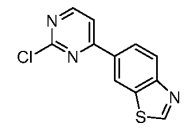
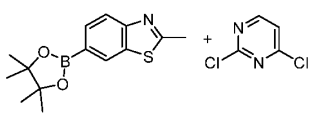
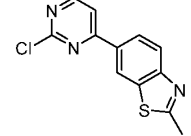
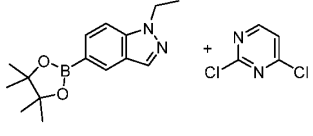
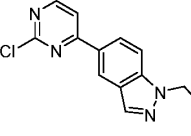
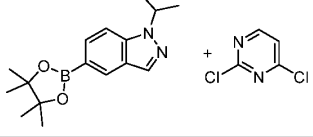
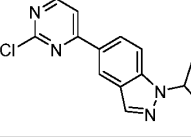
10 实施例 92-112. 中间体 A2-A22 的制备

使用市售或实施例 70-82 制备的硼酯或硼酸化合物和 4,6-二氯嘧啶或 2,4-二氯嘧啶为原料, 参照实施例 91 合成中间体 A1 的方法制备中间体 A2-A22. (表 1)

表 1 中间体 A2-A22

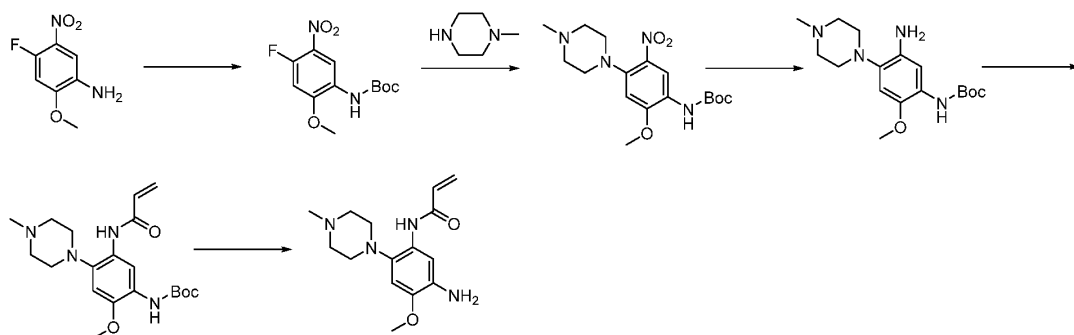
中间体	起始原料	中间体结构	分子离子峰 [M+1] ⁺
A2			245.20
A3			245.23
A4			245.19

A5			313.19
A6			313.20
A7			263.17
A8			263.15
A9			259.20
A10			263.16
A11			245.19
A12			245.20
A13			248.13
A14			248.14

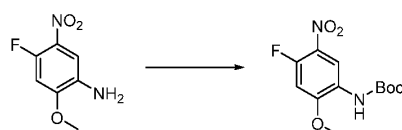
A15			262.7
A16			259.11
A17			273.24
A18			273.16
A19			278.17
A20			292.20
A21			259.31
A22			273.14

实施例 113. 中间体 B1 制备

N-(5-氨基-4-甲氧基-2-(4-甲基哌嗪-1-基)苯基)丙烯酰胺

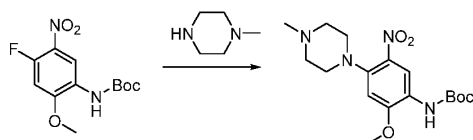


第一步: (4-氟-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯



于 100 mL 三口瓶中加入 4-氟-2-甲氧基-5-硝基苯胺 (3 g, 16 mmol)、DCM (50 mL)、
 5 吡啶 (2.5 g, 32.2 mmol) 和 DMAP (0.19 g, 1.6 mmol), 滴加(Boc)₂O (3.5g, 0.016mol)
 的 DCM 溶液 (10 mL), 滴毕后 40 °C 反应, 反应完毕后减压浓缩, 加入 100 mL 水, 100
 mL 乙酸乙酯, 搅拌分液, 水相用乙酸乙酯萃取 2 次, 合并有机相, 有机相用水 (100 mL
 × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得产品 3.6 g, 收率: 78%。

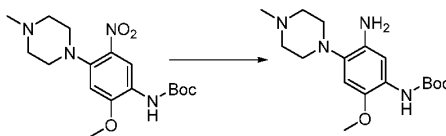
第二步: (2-甲氧基-4-(4-甲基哌嗪-1-基)-5-硝基苯基)氨基甲酸叔丁酯



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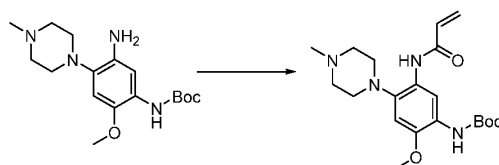
于 250 mL 单口瓶中依次加入 (4-氟-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯 (2.1 g,
 07.3 mmol), DMF (50 mL), N-甲基哌嗪 (808 mg, 8.06 mmol) 和 DIPEA (1.03 g, 8.03
 mmol), 室温搅拌反应, 反应完毕后加入 150 mL 饱和氯化铵水溶液, 50 mL 乙酸乙酯,
 搅拌分液, 水相弃去, 有机相水洗至中性, 饱和食盐水 (30 mL × 2) 洗 2 遍, 无水硫酸
 15 钠干燥 30 min, 过滤, 滤液减压浓缩, 经柱层析纯化, 用 PE/EA = 5/1→1/1 和 DCM/MeOH
 = 10/1 梯度洗脱, 收集产品并减压浓缩得 2.65 g, 收率: 98%。

第三步: (5-氨基-2-甲氧基-4-(4-甲基哌嗪-1-基)苯基)氨基甲酸叔丁酯



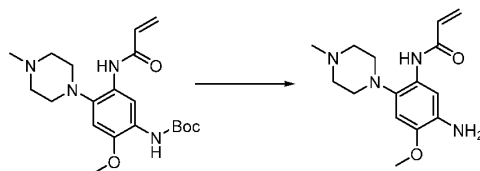
于 250 mL 单口瓶中, 加入 (2-甲氧基-4-(4-甲基哌嗪-1-基)-5-硝基苯基)氨基甲酸叔丁酯 (2.65 g, 7.23 mmol), 甲醇 (10 mL), 10% Pd/C (265 mg), 室温加氢搅拌反应, 反应完毕后, 过滤, 滤液减压浓缩, 得 2.35 g 产品, 收率: 96.7%。

第四步: (5-丙烯酰氨基-2-甲氧基-4-(4-甲基哌嗪-1-基)苯基)氨基甲酸叔丁酯



向 250 mL 三口瓶中加入 (5-氨基-2-甲氧基-4-(4-甲基哌嗪-1-基)苯基)氨基甲酸叔丁酯 (2.3 g, 6.8 mmol) 和 THF (20 mL), 降温至 0 °C, 滴加丙烯酰氯 (680 mg, 7.5 mmol), 滴毕后自然升至室温反应, 反应完毕后, 用饱和碳酸氢钠调 pH 至中性, 加入 DCM (20 mL), 水 (20 mL) 分液, 水相弃去, 有机相用饱和食盐水 (50 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得 2.3 g 产品, 收率: 100%。

第五步: N-(5-氨基-4-甲氧基-2-(4-甲基哌嗪-1-基)苯基)丙烯酰胺

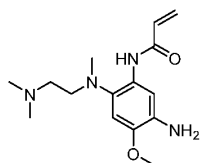


向 250 mL 单口瓶中加入 (5-丙烯酰氨基-2-甲氧基-4-(4-甲基哌嗪-1-基)苯基)氨基甲酸叔丁酯 (1.9 g, 6.88 mmol), 4 mol/L 的盐酸 (16 mL) 和 THF (30 mL), 室温搅拌反应, 反应完毕后用饱和碳酸氢钠水溶液调 pH 至中性, 加入 20 mL 水, 20 mL DCM,

分液，水相用 DCM (20 mL × 2) 萃取 2 次，合并有机相，有机相用水 (20 mL × 2) 洗 2 次，饱和食盐水 (20 mL × 2) 洗 2 次，无水硫酸钠干燥 30 min，过滤，母液减压浓缩干，经柱层析纯化，用 DCM/MeOH = 30/1 洗脱，收集产品并减压浓缩得 472 mg。

实施例 114. 中间体 B2 制备

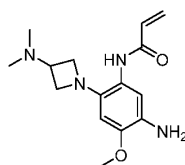
5 N-(5-氨基-2-((2-(二甲基氨基)乙基)(甲基)氨基)-4-甲氧基苯基)丙烯酰胺



将 N,N,N'-三甲基乙二胺代替 N-甲基哌嗪，中间体 B2 的制备过程参见实施例 113。

实施例 115. 中间体 B3 制备

N-(5-氨基-2-(3-(二甲基氨基)氮杂环丁烷-1-基)-4-甲氧基苯基)丙烯酰胺

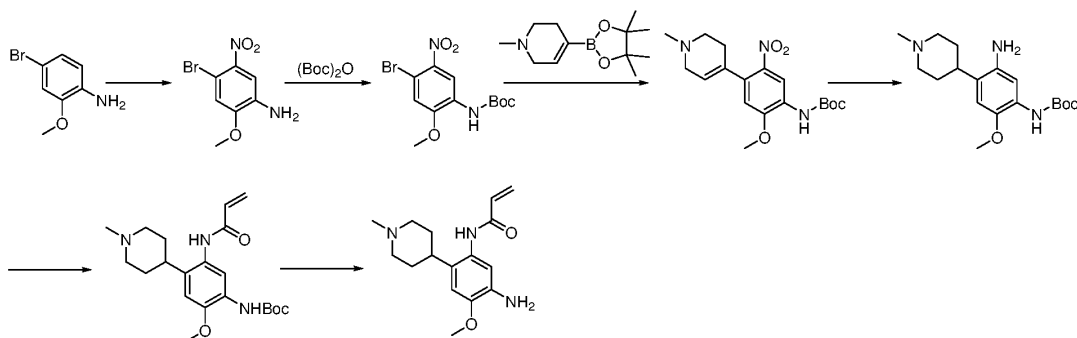


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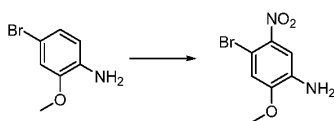
将 3-(二甲基氨基)氮杂环丁烷盐酸盐代替 N-甲基哌嗪，中间体 B3 的制备过程参见实施例 113。

实施例 116. 中间体 B4 制备

N-(5-氨基-4-甲氧基-2-(1-甲基哌啶-4-基)苯基)丙烯酰胺



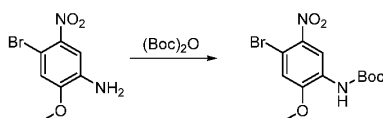
第一步：4-溴-2-甲氧基-5-硝基苯胺



于 100 mL 单口瓶中依次加入 85% 硫酸 (39 mL) 和 4-溴-2-甲氧基苯胺 (5 g, 24.8 mmol),

- 5 降温至 0-5 °C, 分批加入硝酸脲 (3.2 g, 26.1 mmol), 加毕, 恒温反应 45 min。将反应液倒入冰的 50% 氢氧化钠水溶液 (100 mL, pH>8), 控制温度在 5-10 °C 搅拌, 过滤, 滤饼用 100 mL 水淋洗, 烘干。粗品用 50 mL 正己烷打浆 20 min, 过滤, 滤饼烘干得 4.9 g 黄色固体, 收率: 80.19%。

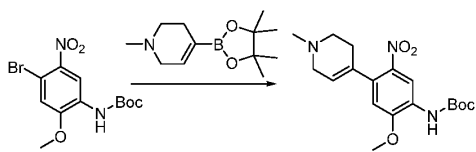
第二步：(4-溴-2-甲氧基-5-硝基苯基) 氨基甲酸叔丁酯



10

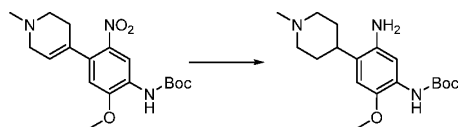
- 于 250 mL 单口瓶中依次加入 4-溴-2-甲氧基-5-硝基苯胺 (4.9 g, 19 mmol), 二氯甲烷 (50 mL), 三乙胺 (4.0 g, 38 mmol), DMAP (243 mg, 1.9 mmol) 和 (Boc)₂O (5.21 g, 23 mmol), 在 25 °C 搅拌反应 4 h。加入 100 mL 水淬灭反应, 水相用二氯甲烷 (100 mL × 2) 萃取 2 次, 合并有机相, 减压浓缩, 得到粗品。粗品经柱层析纯化, 以 PE/EA = 10/1
- 15 洗脱, 收集产品浓缩得 1.4 g 黄色固体, 收率: 20.31%。

第三步：(2-甲氧基-4-(1-甲基-1,2,3,6-四氢吡啶-4-基)-5-硝基苯基) 氨基甲酸叔丁酯



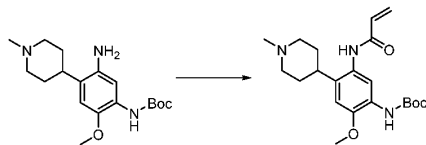
- 氮气保护下，于 100 mL 单口瓶中依次加入 (4-溴-2-甲氧基-5-硝基苯基) 氨基甲酸叔丁酯 (500 mg, 1.44 mmol)，1-甲基-1,2,3,6-四氢吡啶-4-硼酸频哪醇酯 (322 mg, 1.44 mmol)，乙腈 (40 mL)，碳酸钠 (306 mg, 2.88 mmol)，水 (8 mL) 和 $\text{Pd}(\text{PPh}_3)_4$ (167 mg, 0.144 mmol)，在 80 °C 搅拌反应 3.5 h。反应体系降温至室温，加入 50 mL 水，水相用乙酸乙酯萃取 (50 mL $\times$ 2)，合并有机相，减压浓缩，得到粗品。粗品经柱层析纯化，以 $\text{DCM}/\text{MeOH} = 20/1$ 洗脱，收集产品并浓缩，得 480 mg 黄色固体，收率：91.5%。

第四步：(5-氨基-2-甲氧基-4-(1-甲基哌啶-4-基)苯基)氨基甲酸叔丁酯



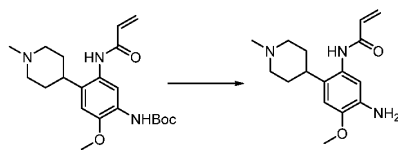
- 于 100 mL 单口瓶中依次加入 (2-甲氧基-4-(1-甲基-1,2,3,6-四氢吡啶-4-基)-5-硝基苯基) 氨基甲酸叔丁酯 (480 mg, 1.32 mmol)，四氢呋喃 (20 mL) 和 Pd/C (50 mg)。室温加氢搅拌反应 12-14 h。过滤，减压浓缩，得到 340 mg 淡黄色油状物，收率：76.8%。

第五步：(5-丙烯酰氨基-2-甲氧基-4-(1-甲基哌啶-4-基)苯基)氨基甲酸叔丁酯



- 以 (5-氨基-2-甲氧基-4-(1-甲基哌啶-4-基)苯基) 氨基甲酸叔丁酯为原料，制备过程参见实施例 113 第四步。

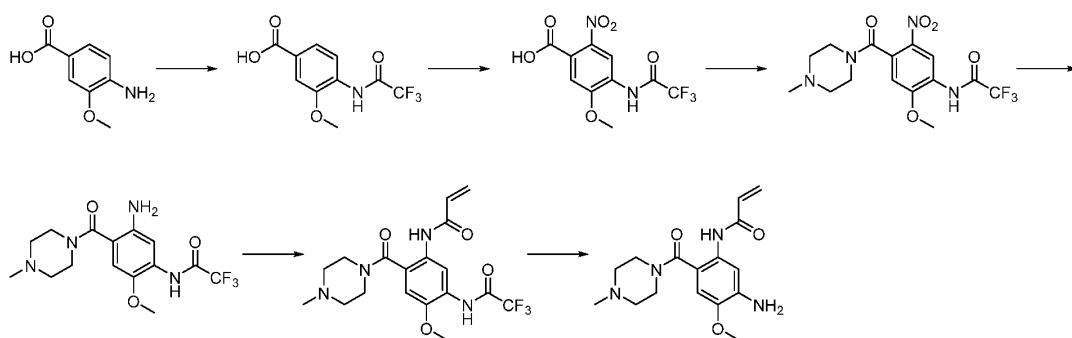
第六步：N-(5-氨基-4-甲氧基-2-(1-甲基哌啶-4-基)苯基)丙烯酰胺



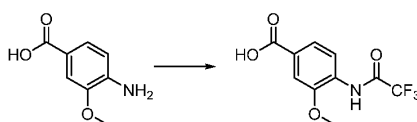
于 100 mL 单口瓶中依次加入 (5-丙烯酰氨基-2-甲氧基-4-(1-甲基哌啶-4-基) 苯基) 氨基甲酸叔丁酯 (300 mg, 0.77 mmol) 和二氯甲烷 (20 mL), 滴加三氟乙酸 (4 mL)。加毕, 室温反应 30 min。向反应液中加入 50 mL 饱和碳酸氢钠水溶液, 分液, 水相用二氯甲烷萃取 (50 mL × 2), 合并有机相, 减压浓缩, 得 170 mg 淡灰色固体, 收率: 76.6%。

实施例 117. 中间体 B5 制备

N-(5-氨基-4-甲氧基-2-(4-甲基哌嗪-1-羰基) 苯基) 丙烯酰胺



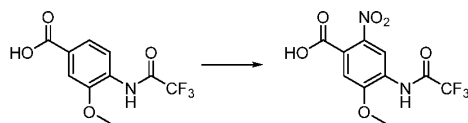
第一步: 3-甲氧基-4-(2,2,2-三氟乙酰氨基) 苯甲酸



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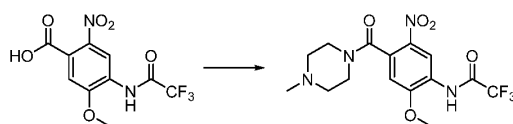
于 500 mL 三口瓶中加入 4-氨基-3-甲氧基苯甲酸 (5 g, 29.9 mmol) 和乙酸乙酯 (200 mL), 冰盐浴降温至 0 °C, 滴加 TFAA (5 mL) 的乙酸乙酯 (5 mL) 溶液。恒温搅拌反应 2 h, 然后升温至室温继续搅拌反应 2 h。加入 200 mL 水, 分液, 水相用乙酸乙酯 (50 mL × 2) 萃取 2 次, 合并有机相, 饱和食盐水 (100 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 抽滤, 滤液减压浓缩得 7.8 g 产品。

第二步: 5-甲氧基-2-硝基-4-(2,2,2-三氟乙酰氨基) 苯甲酸



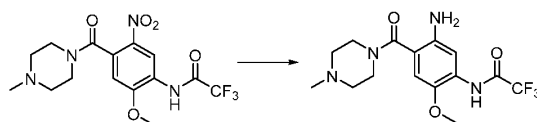
于 100 mL 三口瓶中加入 3-甲氧基-4-(2,2,2-三氟乙酰氨基)苯甲酸 (1 g, 3.8 mmol) 和浓硫酸 (10 mL), 冰盐浴降温至 0 °C, 分批加入硝酸钾 (840 mg, 5.7 mmol), 保温搅拌反应 1 h。将反应液缓慢滴加入 100 mL 冰水中, 再加入 100 mL 乙酸乙酯, 分液, 水相用乙酸乙酯 (50 mL × 2) 萃取 2 次, 合并有机相, 饱和食盐水 (50 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 抽滤, 滤液减压浓缩得 500 mg 产品。

第三步: 2,2,2-三氟-N-(2-甲氧基-4-(4-甲基哌嗪-1-羰基)-5-硝基苯基)乙酰胺



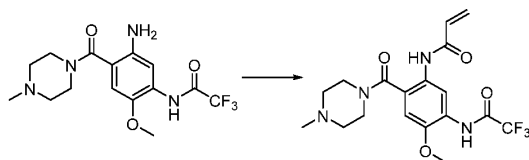
于 100 mL 三口瓶中依次加入 5-甲氧基-2-硝基-4-(2,2,2-三氟乙酰氨基)苯甲酸 (500 mg, 1.622 mmol), 30 mL 二氯甲烷, N-甲基哌嗪 (325 mg, 3.245 mmol), EDCI (436 mg, 2.271 mmol), HOBt (313 mg, 2.044 mmol) 和三乙胺 (656 mg, 6.49 mmol), 室温搅拌反应约 2 h, 将反应液调 pH 至中性, 用乙酸乙酯 (30 mL × 3) 萃取 3 次。合并有机相, 有机相用饱和食盐水 (50 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min。抽滤, 滤液减压浓缩得 250 mg 棕黄色油状产品。

第四步: N-(5-氨基-2-甲氧基-4-(4-甲基哌嗪-1-羰基)苯基)-2,2,2-三氟乙酰胺



以 2,2,2-三氟-N-(2-甲氧基-4-(4-甲基哌嗪-1-羰基)-5-硝基苯基)乙酰胺为原料, 制备过程参见实施例 113 第三步。

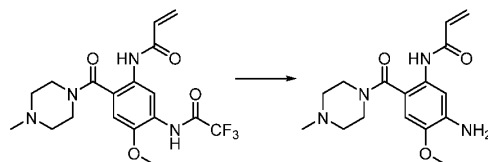
第五步: N-(4-甲氧基-2-(4-甲基哌嗪-1-羰基)-5-(2,2,2-三氟乙酰氨基)苯基)丙烯酰胺



以 N-(5-氨基-2-甲氧基-4-(4-甲基哌嗪-1-羰基)苯基)-2,2,2-三氟乙酰胺为原料,

5 制备过程参见实施例 113 第四步。

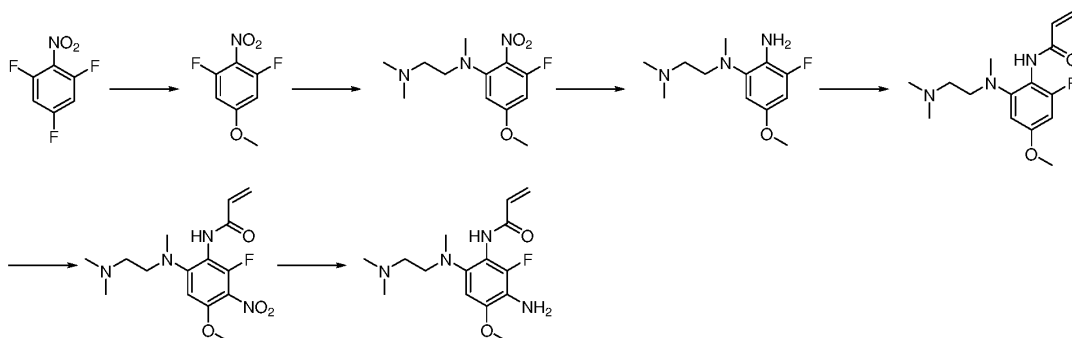
第六步: N-(5-氨基-4-甲氧基-2-(4-甲基哌嗪-1-羰基)苯基)丙烯酰胺



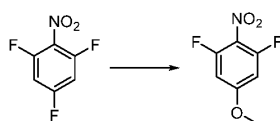
于 250 mL 单口瓶中依次加入 N-(4-甲氧基-2-(4-甲基哌嗪-1-羰基)-5-(2,2,2-三氟乙酰氨基)苯基)丙烯酰胺 (410 mg, 0.99 mmol), 乙腈 (30 mL) 和碳酸钾 (683 mg, 4.95 mmol) 水溶液 (30 mL), 室温搅拌反应过夜。反应完后加入 30 mL 水, 50 mL 二氯甲烷, 萃取分液, 水相用二氯甲烷 (30 mL × 2) 萃取 2 次, 合并有机相, 饱和食盐水 (30 mL × 2) 洗 2 次。无水硫酸钠干燥 30 min, 抽滤, 滤液减压浓缩得 290 mg 产品。

实施例 118. 中间体 B6 制备

N-(3-氨基-6-((2-(二甲基氨基)乙基)(甲基)氨基)-2-氟-4-甲氧基苯基)丙烯酰胺

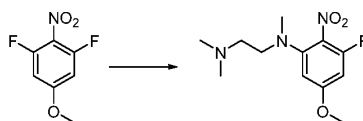


第一步：1,3-二氟-5-甲氧基-2-硝基苯



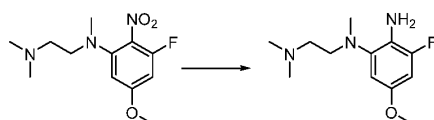
以 1, 3, 5-三氟-2-硝基苯为原料, 制备过程参见实施例 89 第一步。第二步：N1- (3-氟

5-甲氧基-2-硝基苯基)-N1, N2, N2-三甲基乙烷-1,2-二胺



于 100 mL 三口瓶中依次加入 1,3-二氟-5-甲氧基-2-硝基苯(1.27 g, 6.72 mmol)和 DMF
(50 mL), 搅拌溶解, 然后加入 DIPEA(1.13 g, 1.3 eq)和 N,N,N'-三甲基乙二胺 (686 mg,
1 eq), 油浴升温到 50-55 °C 回流反应 4-5 h。自然降温到室温, 将反应液倒入 150 mL 纯
10 化水中, 用乙酸乙酯 (100 mL, 50 mL, 50 mL) 萃取三次, 合并有机相后, 饱和氯化钠
(50 mL × 2) 洗两次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得 1.8 g 油状粗品。

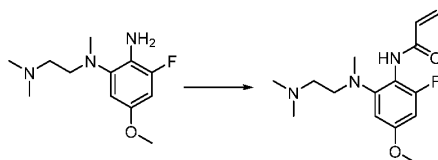
第三步：N1- (2- (二甲基氨基) 乙基) -3-氟-5-甲氧基 N1 甲基苯-1,2-二胺



于 100 mL 单口瓶中依次加入 N1- (3-氟-5-甲氧基-2-硝基苯基)-N1, N2, N2-三甲基
15 乙烷-1,2-二胺(1.8g, 6.63 mmol)和甲醇 (36 mL), 搅拌溶解, 再加入 180 mg Pd/C, 加氢

条件下室温搅拌反应 5-6 h。过滤去掉 Pd/C，滤液减压浓缩得 1.7 g 产品。

第四步：N-（2-（（2-（二甲基氨基）乙基）（甲基）氨基）-6-氟-4-甲氧基苯基）丙烯酰胺



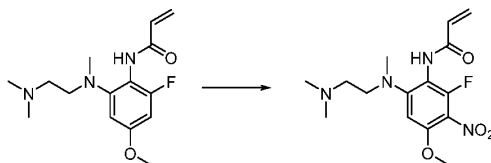
5 于 100 mL 三口瓶中加入 N1-(2-(二甲基氨基)乙基)-3-氟-5-甲氧基 N1 甲基苯-1,2-二胺(920 mg, 3.81 mmol)和干燥 THF (20 mL)，搅拌溶解。反应体系降温到 0-5 °C。

滴加丙烯酰氯 (379 mg, 1.1 eq) 的 THF 溶液 (1 mL)，加毕后保温反应 30 min。将反应液倒入 100 mL 饱和碳酸氢钠水溶液中，用 DCM(50 mL × 3)萃取 3 次，合并有机相，

无水硫酸钠干燥 30 min，过滤，滤液减压浓缩得粗品，粗品经柱层析纯化，用 DCM/MeOH

10 = 20/1→10/1 梯度洗脱，收集产品，减压浓缩得 596 mg 灰色固体。

第五步：N-（6-（（2-（二甲基氨基）乙基）（甲基）氨基）-2-氟-4-甲氧基-3-硝基苯基）丙烯酰胺



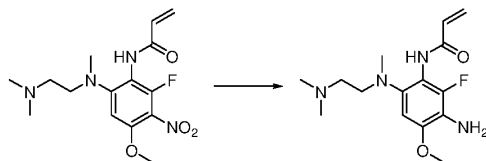
于 100 mL 三口瓶中加入 N-（2-（（2-（二甲基氨基）乙基）（甲基）氨基）-6-氟-4-甲氧基苯基）丙烯酰胺(519 mg, 1.76 mmol)和浓硫酸 (10 mL)，搅拌溶解，反应体系降

温到 0-5 °C。分批缓慢添加硝酸钾 (195 mg, 1.93 mmol) 到体系，加毕后，保温搅拌反应 30 min，然后升温到室温搅拌反应 1-2 h。将反应液缓慢滴加入 200 mL 冰水中淬灭，

用碳酸钠固体调节 pH 到中性，用乙酸乙酯(100 mL × 3)萃取 3 次，合并有机相，无水硫

酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品。粗品经柱层析纯化, 收集产品减压浓缩得 137 mg 产品。

第六步: N-(3-氨基-6-((2-(二甲基氨基)乙基)(甲基)氨基)-2-氟-4-甲氧基苯基)丙烯酰胺



5

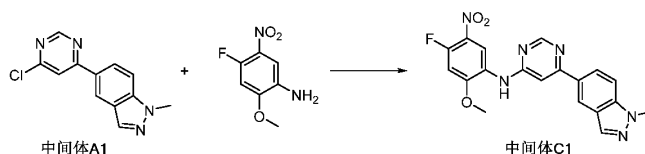
于 100 mL 三口瓶中依次加入 N-(6-((2-(二甲基氨基)乙基)(甲基)氨基)-2-氟-4-甲氧基-3-硝基苯基)丙烯酰胺(137 mg, 0.4 mmol), Fe (135 mg, 6 eq), 氯化铵 (127 mg, 6 eq), 无水乙醇 (8 mL) 和纯化水 (2 mL), 油浴升温到 90-100 °C 反应 2-3 h。

自然降温到室温, 将反应液加入 30 mL 纯化水中, 用乙酸乙酯 (30 mL × 3) 萃取 3 次,

10 合并有机相, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 用 DCM/MeOH = 5/1 洗脱, 收集产品, 减压浓缩得 90 mg 产品。

实施例 119. 中间体 C1 制备

N-(4-氟-2-甲氧基-5-硝基苯基)-6-(1-甲基-1H-吲唑-5-基)嘧啶-4-胺

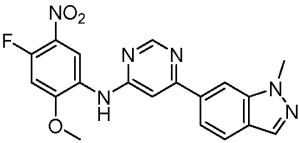
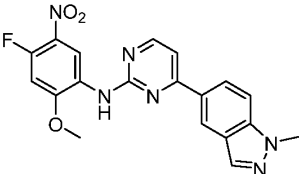
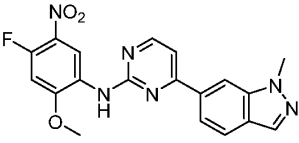
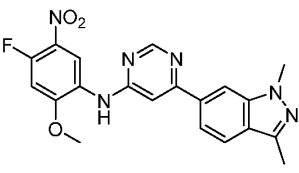
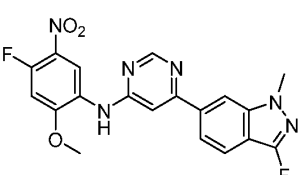
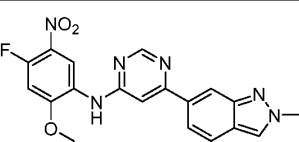


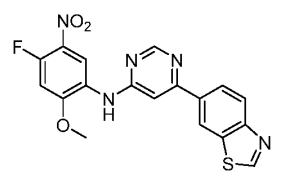
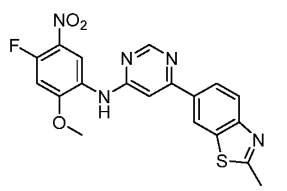
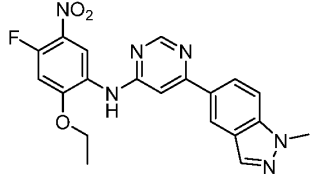
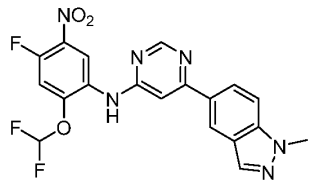
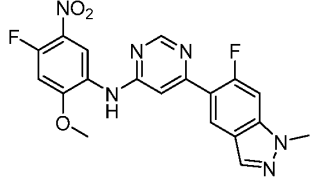
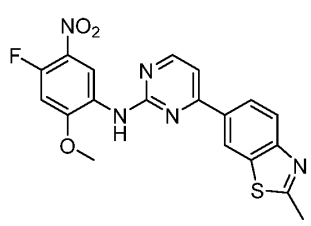
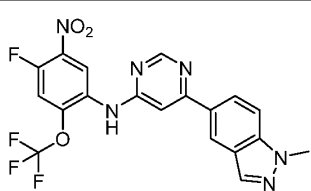
15 于 250 mL 单口瓶中依次加入 4-氟-2-甲氧基-5-硝基苯胺 (2 g, 10.75 mmol), 中间体 A1 (2.38 g, 9.77 mmol), 1,4-二氧六环 (100 mL) 和甲磺酸 (2.82 g, 29.32 mmol)。油浴升温至回流, 搅拌反应约 4 h, 自然降温至室温。室温搅拌 30 min, 过滤, 滤饼用石油醚淋洗, 40-45 °C 鼓风干燥 2-3 h, 得 3.8 g 黄色固体。

实施例 120-149. 中间体 C2-C31 制备

以中间体 A 和取代的硝基苯胺化合物为原料, 应用中间体 C1 合成方法, 制备中间体 C2-C31. (表 2)

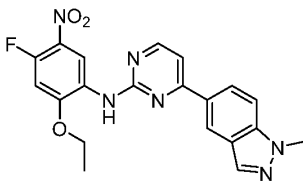
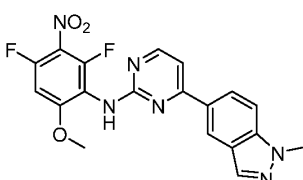
表 2 中间体 C2-C31

实施例	中间体	起始原料	中间体结构	分子离子峰 [M+1] ⁺
120	中间体 C2	A2		395.19
121	中间体 C3	A3		395.13
122	中间体 C4	A4		395.19
123	中间体 C5	A9		409.15
124	中间体 C6	A10		413.12
125	中间体 C7	A12		395.12

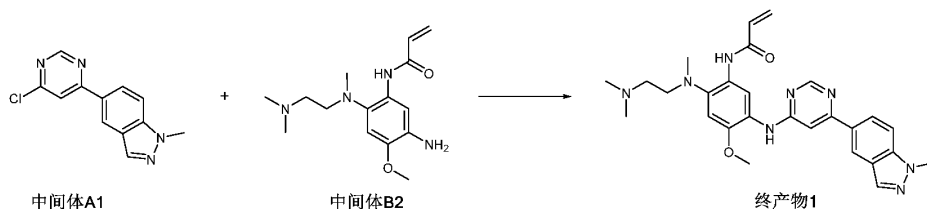
126	中间体 C8	A14		428.15
127	中间体 C9	A15		442.18
128	中间体 C10	A1		409.19
129	中间体 C11	A1		431.25
130	中间体 C12	A7		413.06
131	中间体 C13	A20		412.11
132	中间体 C14	A1		449.34

133	中间体 C15	A4		431.15
134	中间体 C16	A1		413.06
135	中间体 C17	A2		413.22
136	中间体 C18	A4		413.06
137	中间体 C19	A17		423.02
138	中间体 C20	A16		423.15
139	中间体 C21	A22		423.07
140	中间体 C22	A21		423.19

141	中间体 C23	A19		428.25
142	中间体 C24	A1		423.22
143	中间体 C25	A16		445.07
144	中间体 C26	A16		409.10
145	中间体 C27	A3		431.35
146	中间体 C28	A2		431.18
147	中间体 C29	A21		409.20

148	中间体 C30	A3		409.24
149	中间体 C31	A3		413.16

实施例 150. N-(2-(2-二甲基氨基乙基-甲氨基)-4-甲氧基-5-[[6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基]氨基]苯基)丙烯酸酰胺 (终产物 1)



于 100 mL 三口瓶中依次加入中间体 A1 (200 mg, 0.82 mmol), 异丁醇 (15 mL),

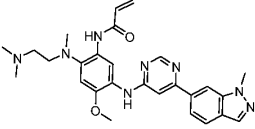
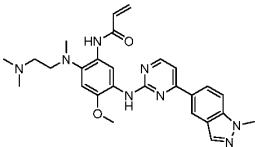
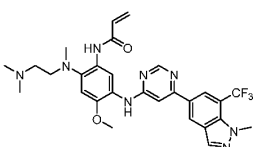
- 5 中间体 B2(218 mg, 0.74 mmol)和甲磺酸(102 mg, 1.06 mmol)。油浴升温至 105-110 °C, 回流反应约 1.5 h, 自然降温至室温。将反应液减压浓缩。粗产品经柱层析纯化, 用二氯甲烷/甲醇/氨水 = 20/1/0.1 洗脱, 收集产品并减压浓缩, 剩余物加正己烷打浆, 抽滤, 滤饼于 40 °C 烘 2 h 得浅白色固体 108 mg。

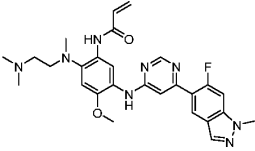
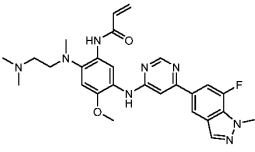
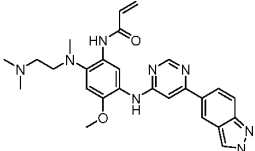
MS (ESI⁺) m/z = 501.33 [M+H]⁺, ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.13 (s, 1H), 8.76 (s, 1H),
 10 8.70 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.38 (s, 1H), 7.02 (s, 1H), 6.37-6.50 (m, 1H), 6.25 (d, *J* = 16.9 Hz, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 4.09 (s, 3H), 3.84 (s, 3H), 2.88 (brs, 2H), 2.73 (s, 3H), 2.33 (brs, 2H), 2.21 (s, 6H)。

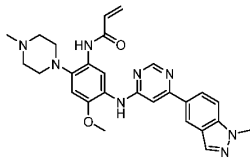
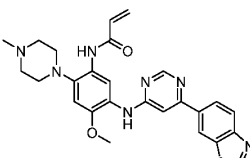
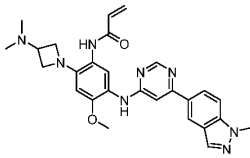
实施例 151-166. 终产物 2-17 的制备

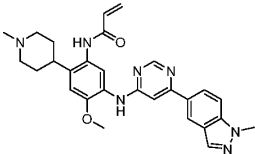
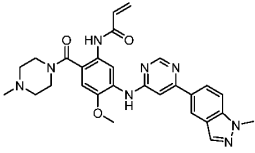
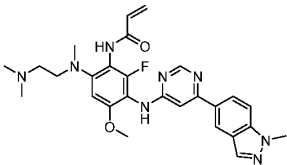
应用上述终产物 **1** 的合成方法, 用中间体 **A** 和 **B** 制备终产物 **2-17** (表 3)。

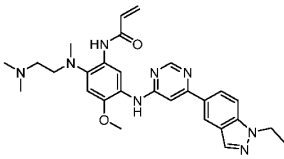
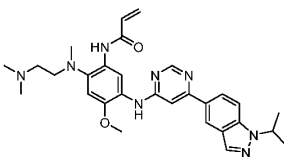
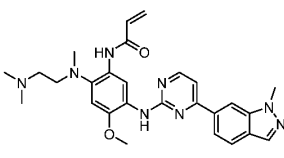
表 3 终产物 **2-17**

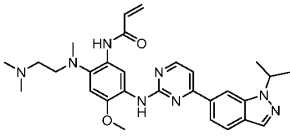
终产物编号	中间体编号	终产物结构	NMR 或 MS
终产物 2	A2+B2		收率: 42.3%. MS (ESI ⁺) m/z = 501.25 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO-d ₆) δ 10.17 (s, 1H), 8.84 (s, 1H), 8.71 (s, 1H), 8.65 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.03 (s, 1H), 6.37-6.50 (m, 1H), 6.22 (d, J = 20.0 Hz, 1H), 5.75 (d, J = 8.0 Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 2.88 (brs, 2H), 2.73 (s, 3H), 2.33 (brs, 2H), 2.22 (s, 6H).
终产物 3	A3+B2		收率: 45%. MS (ESI ⁺) m/z = 501.25 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO-d ₆) δ 10.20 (s, 1H), 9.28 (s, 1H), 8.94 (s, 1H), 8.49 (d, J = 4.0 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.04 (s, 1H), 6.43-6.50 (m, 1H), 6.35 (d, J = 16.0 Hz, 1H), 5.82 (d, J = 8.0 Hz, 1H), 4.10 (s, 3H), 3.89 (s, 3H), 2.88 (brs, 2H), 2.72 (s, 3H), 2.29 (brs, 2H), 2.21 (s, 6H).
终产物 4	A6+B2		MS (ESI ⁺) m/z = 569.18 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO-d ₆) δ 10.14 (s, 1H), 8.87 (s, 1H), 8.83 (s, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 8.51 (s, 1H), 8.43 (s,

			1H), 7.50 (s, 1H), 7.03 (s, 1H), 6.37-6.43 (m, 1H), 6.25 (dd, $J = 1.5$, 16.5 Hz, 1H), 5.76 (dd, $J = 1.5$, 10.0 Hz, 1H), 4.19 (s, 3H), 3.85 (s, 3H), 2.88 (t, $J = 5.5$ Hz, 2H), 2.73 (s, 3H), 2.33 (t, $J = 6.0$ Hz, 2H), 2.21 (s, 6H).
终产物 5	A7+B2		MS (ESI ⁺) $m/z = 519.26$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.07 (s, 1H), 8.97 (s, 1H), 8.60 (s, 2H), 8.47 (d, $J = 7.6$ Hz, 1H), 8.19 (s, 1H), 7.68 (d, $J = 12.0$ Hz, 1H), 7.20 (s, 1H), 7.01 (s, 1H), 6.35-6.43 (m, 1H), 6.22 (d, $J = 15.2$ Hz, 1H), 5.74 (d, $J = 11.5$ Hz, 1H), 4.05 (s, 3H), 3.82 (s, 3H), 2.87 (t, $J = 5.2$ Hz, 2H), 2.72 (s, 3H), 2.32 (t, $J = 5.2$ Hz, 2H), 2.21 (s, 6H).
终产物 6	A8+B2		MS (ESI ⁺) $m/z = 519.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.14 (s, 1H), 8.78 (s, 1H), 8.68 (s, 1H), 8.61 (d, $J = 0.4$ Hz, 1H), 8.33 (d, $J = 0.8$ Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 7.87 (dd, $J = 0.8$, 13.6 Hz, 1H), 7.40 (s, 1H), 7.03 (s, 1H), 6.37-6.44 (m, 1H), 6.26 (dd, $J = 1.6$, 16.8 Hz, 1H), 5.76 (dd, $J = 2.0$, 10.0 Hz, 1H), 4.21 (s, 3H), 3.85 (s, 3H), 2.89 (t, $J = 5.6$ Hz, 2H), 2.73 (s, 3H), 2.34 (d, $J = 5.6$ Hz, 2H), 2.22 (s, 6H).
终产物 7	A11+B2		MS (ESI ⁺) $m/z = 501.18$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.10 (s, 1H), 8.75 (s, 1H), 8.69 (s, 1H), 8.59 (s, 1H), 8.49 (s, 2H), 7.88 (dd, $J = 1.5$, 9.0 Hz, 1H), 7.68 (d, $J = 9.0$ Hz, 1H), 7.36

			(s, 1H), 7.02 (s, 1H), 6.38-6.44 (m, 1H), 6.25 (dd, $J = 1.5, 17.0$ Hz, 1H), 5.75 (dd, $J = 2.0, 10.5$ Hz, 1H), 4.20 (s, 3H), 3.84 (s, 3H), 2.90 (brs, 2H), 2.72 (s, 3H), 2.36 (brs, 2H), 2.24 (brs, 6H).
终产物 8	A1+B1		MS (ESI ⁺) $m/z = 499.29$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.77 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.38 (s, 1H), 6.87 (s, 1H), 6.59-6.70 (m, 1H), 6.23 (d, $J = 20.0$ Hz, 1H), 5.74 (d, $J = 8.0$ Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 2.88 (s, 4H), 2.26 (s, 3H).
终产物 9	A14+B1		MS (ESI ⁺) $m/z = 502.16$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.50 (s, 1H), 9.05 (s, 1H), 8.90 (s, 1H), 8.87 (s, 1H), 8.64 (s, 1H), 8.30 (s, 1H), 8.17-8.21 (m, 2H), 7.43 (s, 1H), 6.88 (s, 1H), 6.60-6.66 (m, 1H), 6.26 (d, $J = 17.5$ Hz, 1H), 5.75 (d, $J = 11.0$ Hz, 1H), 3.86 (s, 3H), 2.89 (t, $J = 4.0$ Hz, 4H), 2.55 (s, 4H), 2.27 (s, 3H).
终产物 10	A1+B3		MS (ESI ⁺) $m/z = 499.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.36 (s, 1H), 8.64 (s, 1H), 8.54 (s, 1H), 8.46 (s, 1H), 8.16 (s, 1H), 8.05 (d, $J = 9.0$ Hz, 1H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.52 (brs, 1H), 7.21 (brs, 1H), 6.44-6.50 (m, 1H), 6.21 (d, $J = 18.5$ Hz, 2H), 5.70 (d, $J = 10.5$ Hz, 1H), 4.08 (s, 3H), 3.96 (t, $J =$

			6.5 Hz, 2H), 3.83 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 3.05 (t, J = 6.0 Hz, 1H), 2.07 (m, 6H).
终产物 11	A1+B4		收率: 18.9%. MS (ESI ⁺) m/z = 498.30 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.58 (s, 1H), 8.77 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 8.18 (s, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.99 (s, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.57 (s, 1H), 6.95 (s, 1H), 6.47-6.60 (m, 1H), 6.24 (d, J = 20.0 Hz, 1H), 5.75 (d, J = 8.8 Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 2.88 (d, J = 10.8 Hz, 2H), 2.51-2.70 (m, 1H), 2.21 (s, 3H), 1.95 (brs, 2H), 1.68-1.80 (m, 4H).
终产物 12	A1+B5		MS (ESI ⁺) m/z = 527.18 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.77 (s, 1H), 8.92 (s, 1H), 8.71 (s, 1H), 8.54 (s, 1H), 8.42 (s, 1H), 8.20 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.71 (s, 1H), 6.95 (s, 1H), 6.47-6.60 (m, 1H), 6.23 (d, J = 16.0 Hz, 1H), 5.74 (d, J = 8.0 Hz, 1H), 4.09 (s, 3H), 3.91 (s, 3H), 3.56 (brs, 2H), 3.23 (brs, 2H), 2.17-2.33 (m, 7H).
终产物 13	A1+B6		MS (ESI ⁺) m/z = 519.23 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.51 (s, 1H), 8.72 (s, 1H), 8.50 (s, 1H), 8.47 (s, 1H), 8.16 (s, 1H), 8.06 (dd, J = 8.9, 1.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 6.94 (s, 1H), 6.57 (s, 1H), 6.46-6.51 (m, 1H), 6.22 (d, J = 16.9 Hz, 1H), 5.73 (d, J =

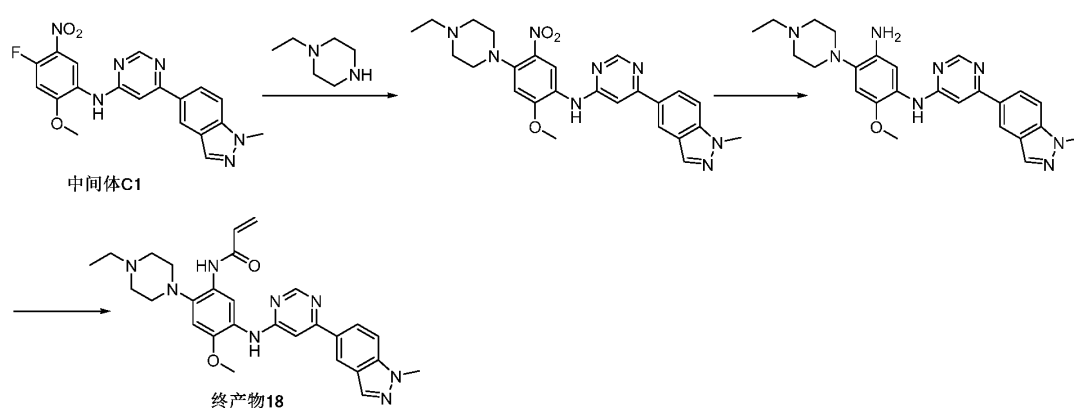
			11.5 Hz, 1H), 4.08 (s, 3H), 3.81 (s, 3H), 3.02 (t, $J = 7.0$ Hz, 2H), 2.80 (s, 3H), 2.43 (q, $J = 7.0$ Hz, 2H), 2.14 (s, 6H).
终产物 14	A16+B2		MS (ESI ⁺) $m/z = 515.17$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.05 (s, 1H), 8.77 (s, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.06 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.79 (d, $J = 9.2$ Hz, 1H), 7.40 (s, 1H), 7.01 (s, 1H), 6.47-6.65 (m, 1H), 6.26 (d, $J = 16.8, 1.2$ Hz, 1H), 5.75 (d, $J = 12.0$ Hz, 1H), 4.48 (q, $J = 7.2$ Hz, 2H), 3.85 (s, 3H), 2.97 (s, 2H), 2.69 (s, 3H), 2.50-2.51 (m, 2H), 2.33 (brs, 6H), 1.42 (t, $J = 7.2$ Hz, 3H).
终产物 15	A17+B2		MS (ESI ⁺) $m/z = 529.20$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.08 (s, 1H), 8.77 (s, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 8.19 (s, 1H), 8.05 (d, $J = 9.2$ Hz, 1H), 7.81 (d, $J = 9.2$ Hz, 1H), 7.39 (s, 1H), 7.01 (s, 1H), 6.45-6.65 (m, 1H), 6.25 (d, $J = 15.6$ Hz, 1H), 5.76 (d, $J = 12.0$ Hz, 1H), 5.00-5.07 (m, 1H), 3.85 (s, 3H), 2.94 (brs, 2H), 2.71 (s, 3H), 2.28-2.50 (m, 8H), 1.50 (d, $J = 5.6$ Hz, 6H).
终产物 16	A4+B2		MS (ESI ⁺) $m/z = 501.16$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.19 (s, 1H), 9.20 (s, 1H), 8.54-8.56 (m, 2H), 8.12 (s, 2H), 8.05 (d, $J = 8.5$ Hz, 1H), 7.86 (d, $J = 8.5$ Hz, 1H), 7.56 (d, $J = 5.0$ Hz, 1H), 7.05 (s, 1H), 6.39-6.45 (m, 1H), 6.25 (d, $J = 17.0$ Hz, 1H), 5.78 (d,

			$J = 10.0 \text{ Hz}$, 1H), 4.12 (s, 3H), 3.88 (s, 3H), 2.89 (m, 2H), 2.72 (s, 3H), 2.31 (brs, 2H), 2.22 (s, 6H).
终产物 17	A18+B2		MS (ESI ⁺) $m/z = 529.23$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.13 (s, 1H), 9.10 (s, 1H), 8.50-8.55 (m, 2H), 8.14 (d, $J = 4.0 \text{ Hz}$, 2H), 8.06 (d, $J = 8.5 \text{ Hz}$, 1H), 7.85 (d, $J = 8.5 \text{ Hz}$, 1H), 7.57 (d, $J = 5.0 \text{ Hz}$, 1H), 7.03 (s, 1H), 6.42-6.45 (m, 1H), 6.28 (d, $J = 13.2 \text{ Hz}$, 1H), 5.77 (d, $J = 11.0 \text{ Hz}$, 1H), 5.10-5.17 (m, 1H), 3.88 (s, 3H), 2.91 (s, 2H), 2.71 (s, 3H), 2.25-2.34 (m, 8H), 1.50 (t, $J = 6.5 \text{ Hz}$, 6H).

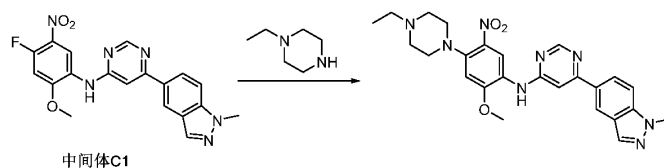
实施例 167. 终产物 18 制备

N-(2-(4-乙基哌嗪-1-基)-4-甲氧基-5-[[6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基]氨基]苯基)丙烯酰胺 (终产物 18)

酰胺 (终产物 18)

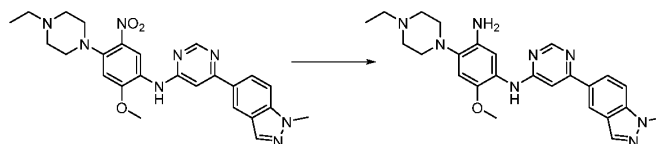


第一步: N-(4-(4-乙基哌嗪-1-基)-2-甲氧基-5-硝基苯基)-6-(1-甲基-1H-吡唑-5-基)嘧啶-4-胺



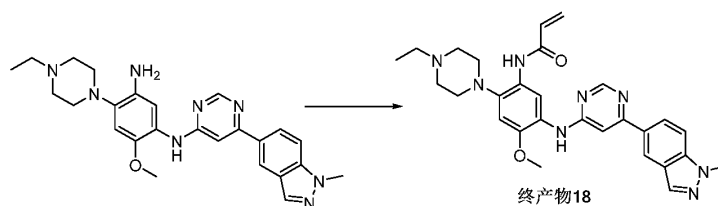
- 于 100 mL 单口瓶中加入 N-(4-氟-2-甲氧基-5-硝基苯基)-6-(1-甲基-1H-咪唑-5-基)嘧啶-4-胺 (中间体 C1) (400 mg, 1.014 mmol) 和 DMF (20 mL), 室温搅拌下加入 1-乙基哌嗪 (150 mg, 1.319 mmol)、DIPEA (196 mg, 1.521 mmol)。油浴升温至 45-50 °C
- 5 搅拌反应, TLC 监测反应进程。反应完全后, 加入水 50 mL, 乙酸乙酯 30 mL, 分液, 水相用乙酸乙酯 (30 mL × 2) 萃取 2 次, 合并有机相, 有机相用水 (50 mL × 2) 洗 2 次, 饱和食盐水 (50 mL × 2) 洗 2 次。无水硫酸钠干燥 30 min, 抽滤, 减压浓缩干得粗品。粗品经柱层析纯化, 用 DCM/MeOH = 10/1 → 5/1 梯度洗脱, 收集产品并减压浓缩得 390 mg, 反应体系中加入的碱可以是 TEA 或 Na₂CO₃/KI。

- 10 第二步: 4-(4-乙基哌嗪-1-基)-6-甲氧基-N1-(6-(1-甲基-1H-咪唑-5-基)嘧啶-4-基)苯-1,3-二胺



- 于 100 mL 单口瓶中依次加入 N-(4-(4-乙基哌嗪-1-基)-2-甲氧基-5-硝基苯基)-6-(1-甲基-1H-咪唑-5-基)嘧啶-4-胺 (390 mg, 0.798 mmol)、DCM (10 mL)、THF (10 mL)
- 15 和 10% Pd/C (80 mg), 室温加氢搅拌反应约 10 h。过滤, 滤液减压浓缩得 300 mg。或使用铁粉和 NH₄Cl 作为还原剂, 乙醇和水作为溶剂, 85-90 °C 搅拌反应还原硝基。

第三步: N-(2-(4-乙基哌嗪-1-基)-4-甲氧基-5-[[6-(1-甲基-1H-咪唑-5-基)嘧啶-4-基]氨基]苯基)丙烯酰胺



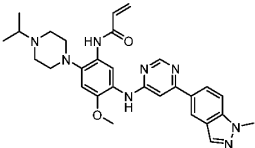
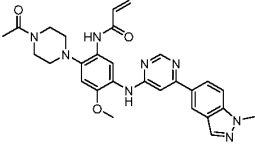
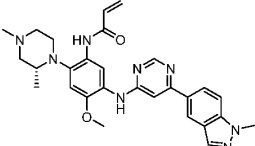
于 100 mL 单口瓶中加入 4-(4-乙基哌嗪-1-基)-6-甲氧基-N1-(6-(1-甲基-1H-咪唑-5-基)嘧啶-4-基)苯-1,3-二胺 (300 mg, 0.654 mmol) 和 THF 溶 (10 mL), 冰盐浴降温, 滴加丙烯酰氯 (65 mg, 0.72 mmol), 滴毕, 体系由清液变浑浊, TLC 监测反应, 原料反应完后加入 30 mL 饱和碳酸氢钠溶液, 再加入二氯甲烷 30 mL, 分液, 水相用二氯甲烷 (30 mL × 2) 萃取 2 次, 合并有机相, 有机相用饱和食盐水 (30 mL × 2) 洗 2 次。无水硫酸钠干燥 30 min, 抽滤, 滤液减压浓缩得粗品。粗品经柱层析纯化, 用 DCM/MeOH = 10/1 洗脱, 收集产品并减压浓缩, 剩余物用正己烷打浆, 抽滤, 滤饼在 45 °C 中鼓风干燥 2 h, 得浅黄色固体 76 mg。

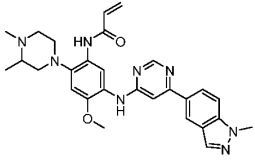
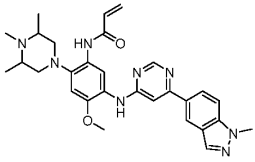
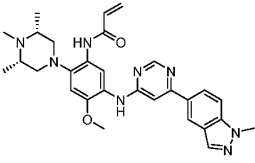
MS (ESI⁺) m/z = 459.21 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.17 (d, *J* = 0.8 Hz, 1H), 8.08 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.38 (s, 1H), 6.89 (s, 1H), 6.58-6.70 (m, 1H), 6.23 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.73 (d, *J* = 10.8 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 2.87 (t, *J* = 4.3 Hz, 4H), 2.58 (brs, 4H), 2.40-2.42 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H).

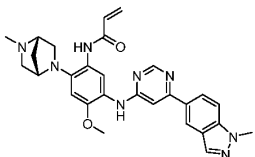
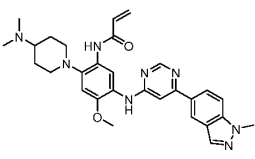
15 实施例 168-411. 终产物 19-262 制备

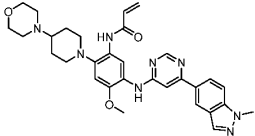
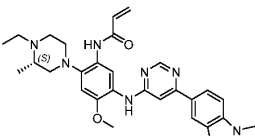
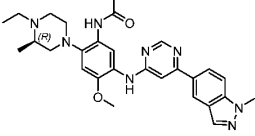
以中间体 C 和市售或实施例 1-69 合成的胺或醇为原料, 运用合成终产物 18 (实施例 167) 的方法制备终产物 19-262. (表 4)

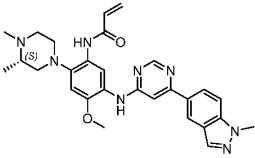
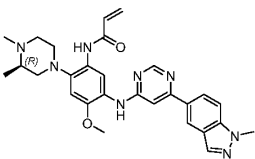
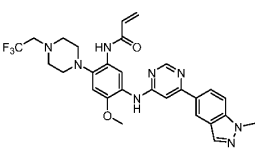
表 4 终产物 19-262

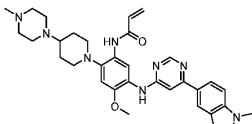
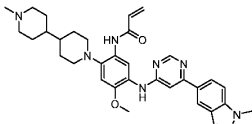
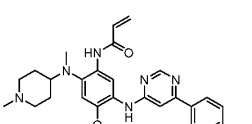
终产物编号	中间体编号	终产物结构	NMR 或 MS
终产物 19	C1		MS (ESI ⁺) m/z = 527.22 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (d, <i>J</i> = 0.4 Hz, 1H), 8.08 (dd, <i>J</i> = 1.2, 8.8 Hz, 1H), 7.75 (d, <i>J</i> = 8.8 Hz, 1H), 7.38 (s, 1H), 6.89 (s, 1H), 6.59-6.67 (m, 1H), 6.23 (dd, <i>J</i> = 1.6, 14.4 Hz, 1H), 5.74 (d, <i>J</i> = 11.6 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 2.87 (d, <i>J</i> = 4.7 Hz, 4H), 2.65-2.80 (m, 5H), 1.02 (d, <i>J</i> = 6.8 Hz, 6H).
终产物 20	C1		MS (ESI ⁺) m/z = 527.27 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.77 (s, 1H), 8.60 (d, <i>J</i> = 1.0 Hz, 1H), 8.50 (d, <i>J</i> = 1.0 Hz, 1H), 8.47 (s, 1H), 8.18 (d, <i>J</i> = 0.5 Hz, 1H), 8.08 (dd, <i>J</i> = 1.5, 9.0 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.41 (s, 1H), 6.91 (s, 1H), 6.65-6.71 (m, 1H), 6.26 (dd, <i>J</i> = 1.5, 17.0 Hz, 1H), 5.76 (d, <i>J</i> = 11.0 Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 3.65 (brs, 4H), 2.82-2.88 (m, 4H), 2.06 (s, 3H).
终产物 21	C1		收率: 18%. MS (ESI ⁺) m/z = 513.22 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.08 (s, 1H), 8.78 (s, 1H), 8.75 (s, 1H), 8.62 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.08 (dd, <i>J</i> = 1.2, 7.2 Hz, 1H), 7.76 (d, <i>J</i> = 7.2 Hz, 1H), 7.45 (s, 1H), 7.03 (s, 1H), 6.57-6.63 (m, 1H), 6.23 (dd, <i>J</i> = 1.2, 13.2

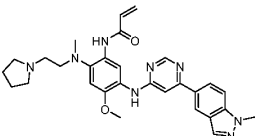
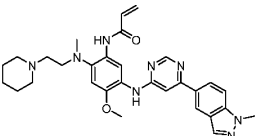
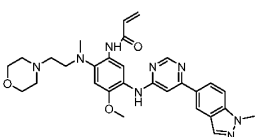
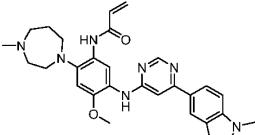
			Hz, 1H), 5.76 (d, $J = 8.4$ Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 3.17 (t, $J = 4.8$ Hz, 1H), 2.72-2.87 (m, 4H), 2.32-2.35 (m, 1H), 2.26 (s, 3H), 2.01-2.06 (t, $J = 10$ Hz, 1H), 0.78 (d, $J = 5.2$ Hz, 3H).
终产物 22	C1		收率: 27%. MS (ESI ⁺) $m/z = 513.25$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 8.18 (s, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 7.75 (d, $J = 8.5$ Hz, 1H), 7.38 (s, 1H), 6.85 (s, 1H), 6.57-6.63 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.0$ Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 2.78-2.94 (m, 4H), 2.25-2.50 (m, 6H), 1.02 (d, $J = 5.5$ Hz, 3H).
终产物 23	C1		MS (ESI ⁺) $m/z = 527.23$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.06 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 8.18 (s, 1H), 8.08 (d, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 1H), 7.38 (s, 1H), 6.84 (s, 1H), 6.57-6.64 (m, 1H), 6.24 (d, $J = 17.2$ Hz, 1H), 5.74 (d, $J = 10.0$ Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 2.89 (d, $J = 10.0$ Hz, 2H), 2.54 (d, $J = 10.8$ Hz, 2H), 2.45 (brs, 2H), 2.24 (s, 3H), 1.03 (d, $J = 5.6$ Hz, 6H).
终产物 24	C1		MS (ESI ⁺) $m/z = 527.17$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 1.0, 9.0$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz,

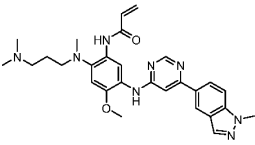
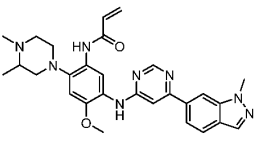
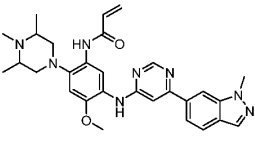
			1H), 7.37 (s, 1H), 6.84 (s, 1H), 6.57-6.63 (m, 1H), 6.23 (d, $J = 16.5$ Hz, 1H), 5.74 (d, $J = 10.5$ Hz, 1H), 4.08 (s, 3H), 3.86 (s, 3H), 2.88 (d, $J = 10.0$ Hz, 2H), 2.53 (d, $J = 10.5$ Hz, 2H), 2.44 (brs, 2H), 2.23 (s, 3H), 1.02 (d, $J = 5.5$ Hz, 6H).
终产物 25	C1		MS (ESI ⁺) $m/z = 511.19$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.32 (s, 1H), 8.63 (s, 1H), 8.56 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 8.06 (dd, $J = 1.2, 8.8$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.59 (s, 1H), 7.25 (s, 1H), 6.42-6.51 (m, 2H), 6.22 (dd, $J = 1.6, 16.8$ Hz, 1H), 5.70 (dd, $J = 2.0, 10.0$ Hz, 1H), 4.20 (s, 1H), 4.08 (s, 3H), 3.83 (s, 3H), 3.39 (d, $J = 8.8$ Hz, 2H), 3.12 (d, $J = 8.8$ Hz, 1H), 2.84 (d, $J = 6.8$ Hz, 1H), 2.75 (d, $J = 9.2$ Hz, 1H), 2.30 (s, 3H), 1.83 (d, $J = 9.2$ Hz, 1H), 1.71 (d, $J = 9.6$ Hz, 1H).
终产物 26	C1		收率: 31.42%. MS (ESI ⁺) $m/z = 527.24$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.37 (s, 1H), 6.86 (s, 1H), 6.65-6.70 (m, 1H), 6.25 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.5$ Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 3.07 (d, $J = 10.5$ Hz, 2H), 2.68 (t, $J = 10.5$ Hz, 2H), 2.50 (s, 1H), 2.25 (s, 6H), 1.85 (d, $J = 11.0$ Hz, 2H), 1.70 (d, $J = 10.5$ Hz, 2H).

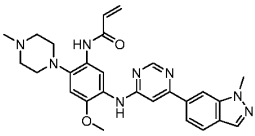
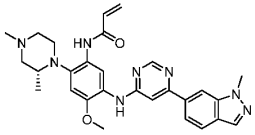
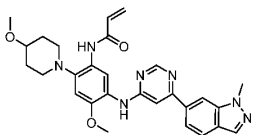
终产物 27	C1		MS (ESI⁺) m/z = 569.23 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.00 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.07 (dd, J = 1.0, 9.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.36 (s, 1H), 6.85 (s, 1H), 6.64-6.70 (m, 1H), 6.24 (d, J = 17.0 Hz, 1H), 5.74 (d, J = 11.0 Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.60 (s, 4H), 3.07 (d, J = 11.0 Hz, 2H), 2.68 (t, J = 11.0 Hz, 2H), 2.49 (s, 4H), 2.20-2.30 (m, 1H), 1.87 (d, J = 11.5 Hz, 2H), 1.69-1.73 (m, 2H).
终产物 28	C1		收率: 23%. MS (ESI⁺) m/z = 527.26 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.04 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 8.18 (d, J = 0.8 Hz, 1H), 8.08 (dd, J = 1.5, 9.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 6.87 (s, 1H), 6.57-6.63 (m, 1H), 6.24 (dd, J = 1.0, 17.0 Hz, 1H), 5.75 (d, J = 11.5 Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 2.95-2.53 (m, 8H), 2.36-2.37 (m, 1H), 1.00-1.05 (m, 6H).
终产物 29	C1		MS (ESI⁺) m/z = 527.22 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.04 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 8.18 (d, J = 1.0 Hz, 1H), 8.08 (dd, J = 1.5, 9.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 6.88 (s, 1H), 6.57-6.63 (m, 1H), 6.23 (d, J = 17.5 Hz, 1H), 5.75 (d, J = 10.0 Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 2.95-2.55 (m, 8H),

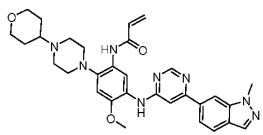
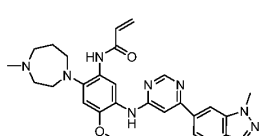
			2.36-2.38 (m, 1H), 1.00-1.05 (m, 6H).
终产物 30	C1		收率: 50%. MS (ESI ⁺) m/z = 513.25 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 8.18 (d, <i>J</i> = 0.5 Hz, 1H), 8.08 (dd, <i>J</i> = 1.5, 9.0 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.38 (s, 1H), 6.85 (s, 1H), 6.57-6.63 (m, 1H), 6.24 (dd, <i>J</i> = 1.5, 17.0 Hz, 1H), 5.75 (d, <i>J</i> = 14.5 Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 2.78-2.92 (m, 4H), 2.46-2.25 (m, 6H), 1.02 (d, <i>J</i> = 6.0 Hz, 3H).
终产物 31	C1		MS (ESI ⁺) m/z = 513.20 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.34 (s, 1H), 8.17 (s, 1H), 8.07 (dd, <i>J</i> = 0.8, 7.2 Hz, 1H), 7.75 (d, <i>J</i> = 7.2 Hz, 1H), 7.37 (s, 1H), 6.85 (s, 1H), 6.57-6.63 (m, 1H), 6.23 (d, <i>J</i> = 13.6 Hz, 1H), 5.73 (d, <i>J</i> = 8.4 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 2.77-2.93 (m, 4H), 2.45-2.24 (m, 6H), 1.01 (d, <i>J</i> = 4.8 Hz, 3H).
终产物 32	C1		收率: 45%. MS (ESI ⁺) m/z = 567.29 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.39 (s, 1H), 8.18 (d, <i>J</i> = 1.0 Hz, 1H), 8.08 (dd, <i>J</i> = 1.5, 9.0 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.40 (s, 1H), 6.93 (s, 1H), 6.60-6.65 (m, 1H), 6.24 (dd, <i>J</i> = 1.5, 17.0 Hz, 1H), 5.75 (d, <i>J</i> = 11.0 Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 3.27

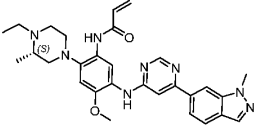
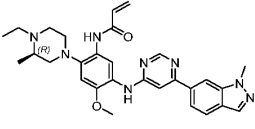
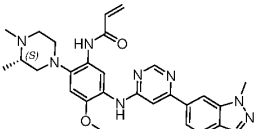
			(q, $J = 10.2$ Hz, 2H), 2.89 (dd, $J = 4.5$, 25.0 Hz, 8H).
终产物 33	C1		MS (ESI ⁺) $m/z = 582.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 1.2$, 7.2 Hz, 1H), 7.75 (d, $J = 7.2$ Hz, 1H), 7.36 (s, 1H), 6.85 (s, 1H), 6.65-6.71 (m, 1H), 6.25 (dd, $J = 1.2$, 13.6 Hz, 1H), 5.74 (d, $J = 9.2$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.06 (d, $J = 8.8$ Hz, 2H), 2.67 (t, $J = 8.8$ Hz, 2H), 2.52-2.53 (m, 4H), 2.26-2.36 (m, 5H), 2.16 (s, 3H), 1.85 (d, $J = 8.8$ Hz, 2H), 1.72-1.74 (m, 2H).
终产物 34	C1		收率: 60.60%. MS (ESI ⁺) $m/z = 581.24$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.99 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 1.2$, 7.2 Hz, 1H), 7.75 (d, $J = 7.2$ Hz, 1H), 7.36 (s, 1H), 6.85 (s, 1H), 6.62-6.66 (m, 1H), 6.24 (dd, $J = 1.2$, 13.6 Hz, 1H), 5.73 (d, $J = 9.2$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.05 (d, $J = 9.2$ Hz, 2H), 2.80 (d, $J = 8.4$ Hz, 2H), 2.63 (t, $J = 9.2$ Hz, 2H), 2.14 (s, 3H), 1.75-1.82 (m, 4H), 1.68 (d, $J = 9.2$ Hz, 2H), 1.46-1.48 (m, 2H), 1.18-1.23 (m, 3H), 1.06-1.10 (m, 1H).
终产物 35	C1		MS (ESI ⁺) $m/z = 527.19$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.13 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.50 (s, 2H), 8.17 (s, 1H), 8.08 (dd, $J = 1.2$, 8.8

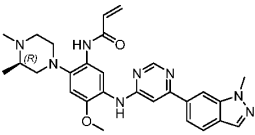
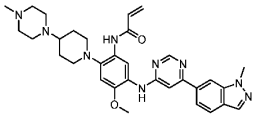
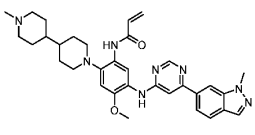
			Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 1H), 7.42 (s, 1H), 6.93 (s, 1H), 6.59-6.93 (m, 1H), 6.23 (dd, $J = 1.6, 16.8$ Hz, 1H), 5.72 (d, $J = 11.6$ Hz, 1H), 4.09 (s, 3H), 3.84 (s, 3H), 2.69-2.76 (m, 3H), 2.64 (s, 3H), 2.12 (s, 3H), 1.54-1.78 (m, 6H).
终产物 36	C1		MS (ESI ⁺) $m/z = 527.17$ [M+H] ⁺ .
终产物 37	C1		MS (ESI ⁺) $m/z = 541.12$ [M+H] ⁺ .
终产物 38	C1		MS (ESI ⁺) $m/z = 543.14$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 1.5, 8.5$ Hz, 1H), 7.76 (d, $J = 8.9$ Hz, 1H), 7.38 (s, 1H), 6.97 (s, 1H), 6.59-6.65 (m, 1H), 6.25 (dd, $J = 1.5, 17.0$ Hz, 1H), 5.76 (d, $J = 11.0$ Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 3.55 (t, $J = 4.5$ Hz, 4H), 3.01 (t, $J = 6.5$ Hz, 2H), 2.72 (s, 3H), 2.34-2.41 (m, 2H).
终产物 39	C1		MS (ESI ⁺) $m/z = 513.13$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.19 (s, 1H), 8.72 (s, 1H), 8.58 (s, 1H), 8.48 (s, 1H), 8.17 (s, 2H), 8.07 (d, $J = 7.2$ Hz, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.35 (s, 1H), 6.85 (s, 1H), 6.57-6.63 (m, 1H), 6.24 (d, $J = 13.2$ Hz, 1H), 5.74 (d, $J = 8.4$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.14-3.17 (m, 4H), 2.75 (brs, 4H), 2.37 (s, 3H), 1.89 (s,

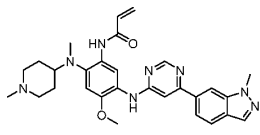
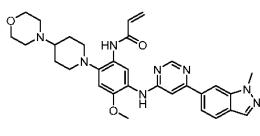
			2H).
终产物 40	C1		收率: 57.6%. MS (ESI ⁺) m/z = 515.17 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.13 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.48 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 8.07 (dd, <i>J</i> = 1.5, 9.0 Hz, 1H), 7.75 (d, <i>J</i> = 9.0 Hz, 1H), 7.37 (s, 1H), 6.91 (s, 1H), 6.62-6.67 (m, 1H), 6.23 (dd, <i>J</i> = 1.5, 17.0 Hz, 1H), 5.72 (d, <i>J</i> = 1.5, 11.5 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 2.85 (t, <i>J</i> = 7.0 Hz, 2H), 2.66 (s, 3H), 2.29 (s, 2H), 2.15 (s, 6H), 1.60-1.66 (m, 2H).
终产物 41	C2		MS (ESI ⁺) m/z = 513.21 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.82 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.11 (d, <i>J</i> = 0.8 Hz, 1H), 7.87 (d, <i>J</i> = 8.4 Hz, 1H), 7.78 (dd, <i>J</i> = 0.8, 8.4 Hz, 1H), 7.48 (s, 1H), 6.87 (s, 1H), 6.57-6.64 (m, 1H), 6.23 (dd, <i>J</i> = 1.2, 16.8 Hz, 1H), 5.75 (dd, <i>J</i> = 2.0, 13.6 Hz, 1H), 4.14 (s, 3H), 3.87 (s, 3H), 2.78-2.91 (m, 4H), 2.43-2.53 (m, 2H), 2.33 (s, 1H), 2.25 (s, 3H), 1.02 (d, <i>J</i> = 6.0 Hz, 3H).
终产物 42	C2		收率: 45%. MS (ESI ⁺) m/z = 527.23 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.06 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 8.33 (s, 1H), 8.10 (d, <i>J</i> = 0.4 Hz, 1H), 7.87 (d, <i>J</i> = 8.4 Hz, 1H), 7.78 (dd, <i>J</i> = 0.8, 8.4 Hz, 1H), 7.47 (s, 1H), 6.84 (s, 1H), 6.57-6.64 (m, 1H), 6.23 (dd, <i>J</i> = 1.2, 16.8 Hz, 1H), 5.74 (dd, <i>J</i> = 2.0,

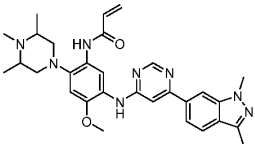
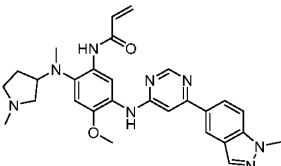
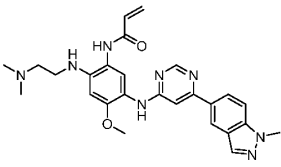
			13.6 Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 2.88 (d, $J = 10.4$ Hz, 2H), 2.54 (d, $J = 10.4$ Hz, 2H), 2.44 (s, 2H), 2.23 (s, 3H), 1.03 (d, $J = 6.0$ Hz, 6H).
终产物 43	C2		收率: 52.04%. MS (ESI ⁺) $m/z = 499.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.36 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.47 (s, 1H), 6.87 (s, 1H), 6.58-6.65 (m, 1H), 6.22 (d, $J = 17.2$ Hz, 1H), 5.73 (d, $J = 10.4$ Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 2.88 (t, $J = 4.4$ Hz, 4H), 2.53 (s, 4H), 2.26 (s, 3H).
终产物 44	C2		收率: 45%. MS (ESI ⁺) $m/z = 513.20$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.09 (s, 1H), 8.85 (s, 1H), 8.77 (s, 1H), 8.67 (s, 1H), 8.34 (s, 1H), 8.11 (d, $J = 0.8$ Hz, 1H), 7.88 (d, $J = 6.8$ Hz, 1H), 7.79 (dd, $J = 1.2, 6.8$ Hz, 1H), 7.54 (s, 1H), 7.04 (s, 1H), 6.57-6.63 (m, 1H), 6.22 (dd, $J = 1.2, 13.6$ Hz, 1H), 5.75 (dd, $J = 0.8, 8.4$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.17 (t, $J = 5.2$ Hz, 1H), 2.71-2.87 (m, 4H), 2.30-2.37 (m, 1H), 2.25 (s, 3H), 1.90-2.10 (m, 1H), 0.78 (d, $J = 4.8$ Hz, 3H).
终产物 45	C2		收率: 45%. MS (ESI ⁺) $m/z = 514.23$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.10 (d, $J = 0.8$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.78

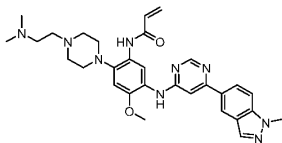
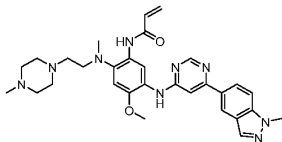
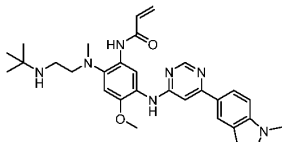
			(dd, $J = 0.8, 8.4$ Hz, 1H), 7.46 (s, 1H), 6.86 (s, 1H), 6.64-6.70 (m, 1H), 6.23 (dd, $J = 1.6, 16.8$ Hz, 1H), 5.74 (dd, $J = 2.4, 13.6$ Hz, 1H), 4.13 (s, 3H), 3.87 (s, 3H), 3.32-3.35 (m, 1H), 3.29 (s, 3H), 2.99-3.02 (m, 2H), 2.68-2.74 (m, 2H), 1.98-2.01 (m, 2H), 1.70-1.73 (m, 2H).
终产物 46	C2		收率: 54.29%. MS (ESI ⁺) $m/z = 569.27$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.10 (d, $J = 0.8$ Hz, 1H), 7.87 (d, $J = 6.8$ Hz, 1H), 7.78 (dd, $J = 1.2, 6.8$ Hz, 1H), 7.48 (s, 1H), 6.90 (s, 1H), 6.60-6.66 (m, 1H), 6.21 (dd, $J = 1.2, 13.6$ Hz, 1H), 5.74 (dd, $J = 3.2, 9.2$ Hz, 1H), 4.13 (s, 3H), 3.92 (dd, $J = 2.4, 8.4$ Hz, 2H), 3.86 (s, 3H), 3.25-3.33 (m, 2H), 2.89 (t, $J = 3.2$ Hz, 4H), 2.70 (brs, 4H), 2.40-2.50 (m, 1H), 1.76 (d, $J = 10.8$ Hz, 2H), 1.40-1.48 (m, 2H).
终产物 47	C2		MS (ESI ⁺) $m/z = 513.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.20 (s, 1H), 8.79 (s, 1H), 8.63 (s, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 8.10 (s, 1H), 7.87 (d, $J = 6.8$ Hz, 1H), 7.78 (d, $J = 7.2$ Hz, 1H), 7.45 (s, 1H), 6.86 (s, 1H), 6.57-6.63 (m, 1H), 6.23 (d, $J = 13.6$ Hz, 1H), 5.74 (d, $J = 8.8$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.16-3.18 (m, 4H), 2.73 (brs, 4H), 2.37 (s, 3H), 1.89 (s, 2H).

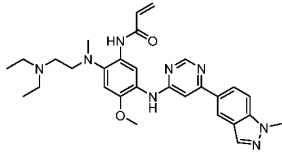
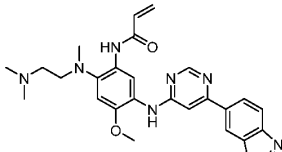
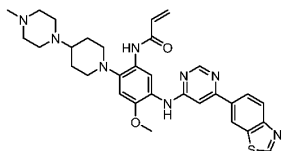
终产物 48	C2		收率: 8%. MS (ESI⁺) m/z = 527.26 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 8.82 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, <i>J</i> = 8.5 Hz, 1H), 7.79 (d, <i>J</i> = 8.5 Hz, 1H), 7.48 (s, 1H), 6.88 (s, 1H), 6.57-6.63 (m, 1H), 6.23 (d, <i>J</i> = 17.0 Hz, 1H), 5.75 (d, <i>J</i> = 10.0 Hz, 1H), 4.14 (s, 3H), 3.87 (s, 3H), 2.51-2.95 (m, 8H), 2.37 (s, 1H), 1.03 (d, <i>J</i> = 13.5 Hz, 6H).
终产物 49	C2		收率: 24.6%. MS (ESI⁺) m/z = 527.20 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 8.37 (s, 1H), 8.10 (d, <i>J</i> = 0.4 Hz, 1H), 7.87 (d, <i>J</i> = 6.4 Hz, 1H), 7.78 (dd, <i>J</i> = 0.8, 6.8 Hz, 1H), 7.48 (s, 1H), 6.88 (s, 1H), 6.57-6.63 (m, 1H), 6.23 (dd, <i>J</i> = 1.2, 13.6 Hz, 1H), 5.73 (d, <i>J</i> = 8.8 Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 2.96 (d, <i>J</i> = 9.2 Hz, 1H), 2.76-2.88 (m, 4H), 2.66 (s, 1H), 2.52-2.57 (m, 2H), 2.37-2.39 (m, 1H), 1.01-1.05 (m, 6H).
终产物 50	C2		收率: 31%. MS (ESI⁺) m/z = 513.21 [M+H]⁺. ¹H NMR (300 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 8.82 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, <i>J</i> = 8.5 Hz, 1H), 7.78 (d, <i>J</i> = 8.5 Hz, 1H), 7.48 (s, 1H), 6.87 (s, 1H), 6.61-6.70 (m, 1H), 6.23 (d, <i>J</i> = 17.0 Hz, 1H), 5.74 (d, <i>J</i> = 11.9 Hz, 1H), 4.17 (s, 3H), 3.87 (s, 3H), 2.70-2.90 (m, 4H), 2.25-2.46 (m, 6H), 1.02 (d, <i>J</i> = 6.1 Hz,

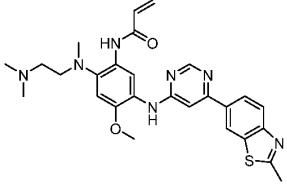
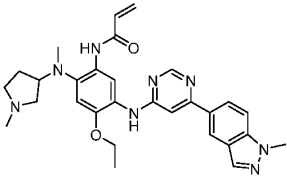
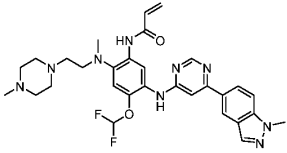
			3H).
终产物 51	C2		收率: 35.7%. MS (ESI ⁺) m/z = 513.23 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.11 (d, <i>J</i> = 0.4 Hz, 1H), 7.87 (d, <i>J</i> = 6.8 Hz, 1H), 7.78 (dd, <i>J</i> = 0.8, 6.8 Hz, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 6.58-6.64 (m, 1H), 6.23 (dd, <i>J</i> = 1.2, 13.6 Hz, 1H), 5.74 (d, <i>J</i> = 8.8 Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 2.78-2.94 (m, 4H), 2.44 (t, <i>J</i> = 8.0 Hz, 2H), 2.32 (s, 1H), 2.25 (s, 3H), 1.01 (d, <i>J</i> = 4.8 Hz, 3H).
终产物 52	C2		MS (ESI ⁺) m/z = 582.27 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.10 (d, <i>J</i> = 0.4 Hz, 1H), 7.87 (d, <i>J</i> = 6.8 Hz, 1H), 7.78 (dd, <i>J</i> = 0.8, 6.8 Hz, 1H), 7.46 (s, 1H), 6.85 (s, 1H), 6.65-6.71 (m, 1H), 6.22 (dd, <i>J</i> = 0.4, 13.6 Hz, 1H), 5.74 (d, <i>J</i> = 9.2 Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.07 (d, <i>J</i> = 8.0 Hz, 2H), 2.68 (t, <i>J</i> = 9.2 Hz, 2H), 2.56 (s, 4H), 2.30-2.40 (m, 5H), 2.20 (s, 3H), 1.85 (d, <i>J</i> = 8.8 Hz, 2H), 1.70-1.75 (m, 2H).
终产物 53	C2		收率: 36.4%. MS (ESI ⁺) m/z = 581.25 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.80 (s, 1H), 8.63 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.87 (d, <i>J</i> = 6.8 Hz, 1H), 7.78 (dd, <i>J</i> = 0.8, 6.8 Hz, 1H), 7.46 (s, 1H), 6.85 (s, 1H),

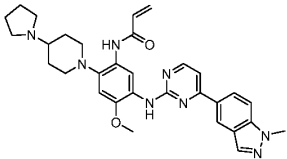
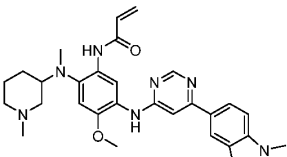
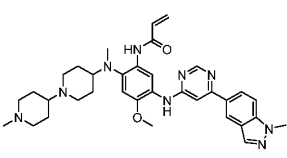
			6.62-6.68 (m, 1H), 6.23 (dd, $J = 1.2, 13.6$ Hz, 1H), 5.73 (d, $J = 8.8$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.05 (d, $J = 9.2$ Hz, 2H), 2.82 (d, $J = 8.4$ Hz, 2H), 2.63 (t, $J = 9.2$ Hz, 2H), 2.16 (s, 3H), 1.83 (t, $J = 8.0$ Hz, 2H), 1.76 (d, $J = 9.2$ Hz, 2H), 1.69 (d, $J = 10.0$ Hz, 2H), 1.47 (q, $J = 7.6$ Hz, 2H), 1.16-1.23 (m, 3H), 1.05-1.10 (m, 1H).
终产物 54	C2		MS (ESI ⁺) $m/z = 527.25$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.36 (s, 1H), 8.68 (s, 1H), 8.24 (s, 1H), 8.07 (s, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.54 (s, 1H), 7.21 (s, 1H), 6.71 (s, 1H), 6.45-6.70 (m, 2H), 6.22 (dd, $J = 2.0, 17.0$ Hz, 1H), 5.73 (dd, $J = 1.5, 10.0$ Hz, 1H), 4.96 (s, 1H), 4.10 (s, 3H), 3.77 (s, 3H), 3.43 (brs, 1H), 3.32 (s, 3H), 2.77 (brs, 2H), 2.22 (s, 3H), 2.14 (s, 2H), 1.95-2.01 (m, 2H), 1.46-1.54 (m, 2H).
终产物 55	C2		MS (ESI ⁺) $m/z = 569.23$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.11 (d, $J = 0.5$ Hz, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.79 (dd, $J = 1.0, 8.5$ Hz, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 6.65-6.71 (m, 1H), 6.24 (dd, $J = 1.5, 17.0$ Hz, 1H), 5.74 (d, $J = 11.5$ Hz, 1H), 4.14 (s, 3H), 3.85 (s, 3H), 3.60 (t, $J = 4.5$ Hz, 4H), 3.08 (d, $J = 7.5$ Hz, 2H), 2.67 (t, $J = 11.5$ Hz, 2H), 2.52 (s, 4H), 2.26 (t, $J = 11.0$ Hz, 1H), 1.88 (d, $J = 11.0$ Hz, 2H),

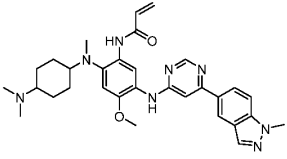
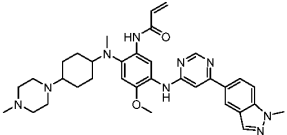
			1.69-1.74 (m, 2H).
终产物 56	C5		MS (ESI ⁺) m/z = 541.24 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.80 (s, 1H), 8.63 (s, 1H), 8.39 (s, 1H), 8.25 (s, 1H), 7.82 (d, <i>J</i> = 8.5 Hz, 1H), 7.74 (dd, <i>J</i> = 1.0, 8.5 Hz, 1H), 7.48 (s, 1H), 6.85 (s, 1H), 6.58-6.64 (m, 1H), 6.23 (dd, <i>J</i> = 1.0, 17.0 Hz, 1H), 5.74 (dd, <i>J</i> = 4.5, 15.5 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 2.88 (d, <i>J</i> = 10.5 Hz, 2H), 2.54 (d, <i>J</i> = 10.5 Hz, 2H), 2.50 (d, <i>J</i> = 1.7 Hz, 3H), 2.44 (brs, 2H), 2.23 (s, 3H), 1.03 (d, <i>J</i> = 6.0 Hz, 6H).
终产物 57	C1		收率: 54%. MS (ESI ⁺) m/z = 513.15 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (s, 1H), 8.76 (s, 1H), 8.63 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 8.08 (d, <i>J</i> = 9.0 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.43 (s, 1H), 6.98 (s, 1H), 6.58-6.64 (m, 1H), 6.24 (d, <i>J</i> = 17.0 Hz, 1H), 5.75 (d, <i>J</i> = 10.5 Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 3.59-3.64 (m, 1H), 2.53-2.58 (m, 4H), 2.46-2.50 (m, 3H), 2.26 (s, 3H), 1.90-1.97 (m, 1H), 1.72-1.79 (m, 1H).
终产物 58	C1		MS (ESI ⁺) m/z = 487.11 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.43 (s, 1H), 8.59 (s, 1H), 8.53 (s, 1H), 8.44 (s, 1H), 8.16 (s, 1H), 8.04 (dd, <i>J</i> = 1.2, 9.0 Hz, 1H), 7.72 (d, <i>J</i> = 9.0 Hz, 1H), 7.48 (s, 1H), 7.14 (s, 1H), 6.44-6.50 (m, 1H), 6.41

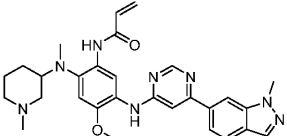
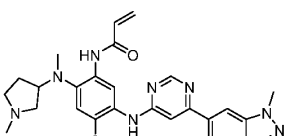
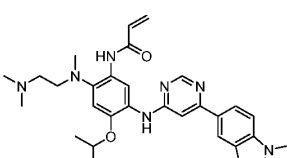
			(s, 1H), 6.22 (dd, $J = 2.0, 17.0$ Hz, 1H), 5.71 (dd, $J = 2.0, 10.5$ Hz, 1H), 4.89 (s, 1H), 4.07 (s, 3H), 3.83 (s, 3H), 3.20 (q, $J = 6.0$ Hz, 2H), 2.49 (s, 2H), 2.21 (s, 6H).
终产物 59	C1		MS (ESI ⁺) $m/z = 556.19$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.78 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 8.18 (s, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.40 (s, 1H), 6.88 (s, 1H), 6.60-6.66 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.5$ Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 2.88 (s, 4H), 2.64 (s, 4H), 2.53 (s, 4H), 2.28 (s, 6H).
终产物 60	C1		MS (ESI ⁺) $m/z = 556.14$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 1.5, 9.0$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.38 (s, 1H), 6.96 (s, 1H), 6.58-6.64 (m, 1H), 6.23 (dd, $J = 1.5, 18.5$ Hz, 1H), 5.74 (s, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 2.98 (t, $J = 6.5$ Hz, 2H), 2.70 (s, 3H), 2.30-2.39 (m, 10H), 2.13 (s, 3H).
终产物 61	C1		收率: 65.4%. MS (ESI ⁺) $m/z = 529.14$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.46 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.55 (s, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 8.07 (d, $J = 8.5$ Hz, 1H), 7.75 (d, $J = 8.5$ Hz, 1H), 7.35 (s, 1H), 6.94 (s, 1H), 6.64-6.69 (m, 1H), 6.25 (d, $J = 17.5$ Hz, 1H), 5.73 (d, $J = 9.0$ Hz, 1H), 4.09 (s,

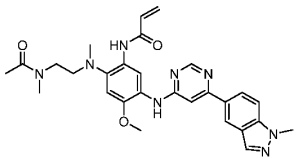
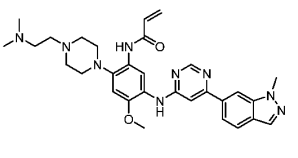
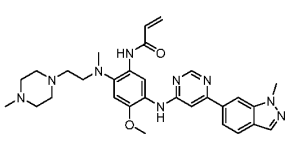
			3H), 3.85 (s, 3H), 3.32 (s, 1H), 2.89 (s, 2H), 2.68 (s, 3H), 2.64 (s, 2H), 1.04 (s, 9H).
终产物 62	C1		收率: 35.0%. MS (ESI ⁺) m/z = 529.13 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.73 (s, 1H), 8.75 (s, 1H), 8.60 (s, 2H), 8.49 (s, 1H), 8.16 (s, 1H), 8.07 (dd, <i>J</i> = 1.2, 8.8 Hz, 1H), 7.74 (d, <i>J</i> = 9.2 Hz, 1H), 7.35 (s, 1H), 6.98 (s, 1H), 6.43-6.50 (m, 1H), 6.25 (d, <i>J</i> = 16.0 Hz, 1H), 5.75 (d, <i>J</i> = 10.8 Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 2.86 (s, 2H), 2.72 (s, 3H), 2.53 (s, 6H), 0.95 (t, <i>J</i> = 6.8 Hz, 6H).
终产物 63	C8		收率: 29.7%. MS (ESI ⁺) m/z = 504.13 [M+H] ⁺ . ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 10.13 (s, 1H), 9.50 (s, 1H), 8.90 (s, 1H), 8.86 (s, 1H), 8.65 (s, 2H), 8.19 (s, 2H), 7.44 (s, 1H), 7.03 (s, 1H), 6.37-6.47 (m, 1H), 6.27 (d, <i>J</i> = 16.2 Hz, 1H), 5.77 (d, <i>J</i> = 9.6 Hz, 1H), 3.85 (s, 3H), 2.89 (brs, 2H), 2.73 (s, 3H), 2.36 (brs, 2H), 2.24 (s, 6H).
终产物 64	C8		收率: 22.7%. MS (ESI ⁺) m/z = 585.21 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.49 (s, 1H), 9.01 (s, 1H), 8.90 (s, 1H), 8.85 (s, 1H), 8.63 (s, 1H), 8.32 (s, 1H), 8.19 (s, 2H), 7.41 (s, 1H), 6.86 (s, 1H), 6.66-6.72 (m, 1H), 6.26 (d, <i>J</i> = 16.5 Hz, 1H), 5.75 (d, <i>J</i> = 11.0 Hz, 1H), 3.84 (s, 3H), 3.07 (d, <i>J</i> = 11.5 Hz, 2H), 2.68 (t, <i>J</i> = 11.0 Hz, 2H), 2.52 (s, 4H), 2.26-2.36 (m, 5H), 2.16 (s, 3H), 1.85 (d, <i>J</i> = 11.5

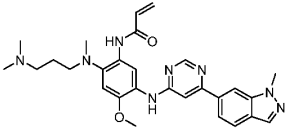
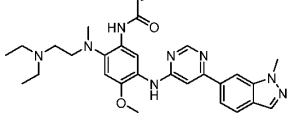
			Hz, 2H), 1.68-1.74 (m, 2H).
终产物 65	C9		MS (ESI ⁺) m/z = 518.26 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.12 (s, 1H), 8.82 (s, 1H), 8.75 (d, J = 1.6 Hz, 1H), 8.64 (s, 1H), 8.62 (s, 1H), 8.11 (dd, J = 1.6, 8.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.40 (s, 1H), 7.02 (s, 1H), 6.37-6.45 (m, 1H), 6.24 (dd, J = 1.6, 16.8 Hz, 1H), 5.75 (dd, J = 2.0, 12.0 Hz, 1H), 3.84 (s, 3H), 2.89 (s, 2H), 2.83 (s, 3H), 2.72 (s, 3H), 2.34 (m, 2H), 2.22 (s, 6H).
终产物 66	C10		MS (ESI ⁺) m/z = 527.31 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.32 (s, 1H), 8.64 (s, 1H), 8.62 (s, 1H), 8.60 (s, 1H), 8.53 (s, 1H), 8.18 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.42 (s, 1H), 6.97 (s, 1H), 6.56-6.68 (m, 1H), 6.25 (d, J = 17.1 Hz, 1H), 5.75 (d, J = 10.0 Hz, 1H), 4.09-4.14 (m, 5H), 3.61 (s, 1H), 2.58 (s, 3H), 2.53-2.51 (m, 1H), 2.49-2.48 (m, 1H), 2.41 (t, J = 6.3 Hz, 2H), 2.23 (s, 3H), 1.89-1.91 (m, 1H), 1.73-1.75 (m, 1H), 1.32 (t, J = 6.9 Hz, 3H).
终产物 67	C11		MS (ESI ⁺) m/z = 592.26 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.44 (s, 1H), 9.03 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.45 (s, 1H), 8.17 (s, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.32 (s, 0.3H), 7.13 (s, 0.5H), 7.11 (s, 1H), 6.95 (s, 0.2H),

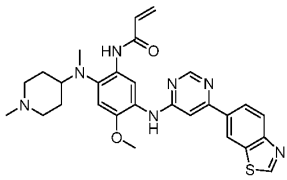
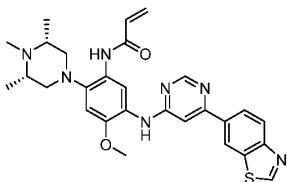
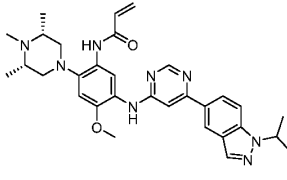
			6.61-6.68 (m, 1H), 6.6 (d, $J = 16.8$ Hz, 1H), 5.79 (d, $J = 10.0$ Hz, 1H), 4.08 (s, 3H), 2.97 (s, 2H), 2.69 (s, 3H), 2.27-2.39 (m, 10H), 2.11 (s, 3H).
终产物 68	C3		MS (ESI ⁺) $m/z = 553.46$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 9.00 (s, 1H), 8.87 (s, 1H), 8.48 (d, $J = 4.8$ Hz, 1H), 8.28 (d, $J = 8.8$ Hz, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.48 (d, $J = 5.2$ Hz, 1H), 6.87 (s, 1H), 6.68-6.75 (m, 1H), 6.32 (d, $J = 16.4$ Hz, 1H), 5.79 (d, $J = 10.4$ Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.00 (d, $J = 10.4$ Hz, 2H), 2.70 (t, $J = 10.8$ Hz, 2H), 2.50 (s, 4H), 2.09 (s, 1H), 1.94 (d, $J = 11.2$ Hz, 2H), 1.69 (s, 6H).
终产物 69	C1		MS (ESI ⁺) $m/z = 527.16$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.57 (s, 1H), 8.74 (s, 1H), 8.61 (s, 1H), 8.56 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.76 (d, $J = 7.2$ Hz, 1H), 7.43 (s, 1H), 6.99 (s, 1H), 6.49-6.55 (m, 1H), 6.23 (d, $J = 13.6$ Hz, 1H), 5.73 (d, $J = 8.4$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 2.90 (s, 1H), 2.65 (s, 3H), 2.57 (s, 1H), 2.00-2.02 (m, 4H), 1.98-1.99 (d, $J = 2.0$ Hz, 2H), 1.72 (d, $J = 5.6$ Hz, 2H), 1.40-1.51 (m, 2H).
终产物 70	C1		MS (ESI ⁺) $m/z = 610.18$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.12 (s, 1H), 8.73 (s, 1H), 8.59 (s, 1H), 8.51 (s, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 8.07 (dd, J

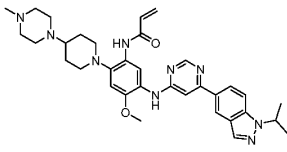
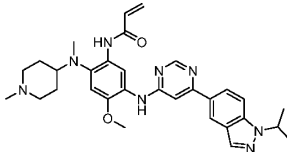
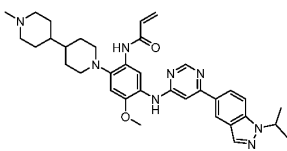
			= 9.2, 1.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.41 (s, 1H), 6.92 (s, 1H), 6.59-6.70 (m, 1H), 6.24 (dd, J = 16.8, 1.6 Hz, 1H), 5.71 (dd, J = 10.0, 1.6 Hz, 1H), 4.08 (s, 3H), 3.83 (s, 3H), 2.85 (d, J = 11.2 Hz, 2H), 2.74 (d, J = 11.2 Hz, 2H), 2.67 (s, 1H), 2.63 (s, 3H), 2.04-2.10 (m, 4H), 2.00 (t, J = 11.6 Hz, 2H), 1.79 (t, J = 11.2 Hz, 2H), 1.70 (d, J = 10.8 Hz, 2H), 1.62 (d, J = 11.6 Hz, 2H), 1.50-1.52 (m, 2H), 1.36-1.38 (m, 2H)
终产物 71	C1		收率: 18.79%. MS (ESI⁺) m/z = 555.19 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.10 (s, 1H), 8.73 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.43 (s, 1H), 8.18 (s, 1H), 8.08 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 6.8 Hz, 1H), 7.41 (s, 1H), 6.89 (s, 1H), 6.59-6.65 (m, 1H), 6.24 (d, J = 13.2 Hz, 1H), 5.73 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 3.84 (s, 3H), 2.65-2.69 (m, 1H), 2.64 (s, 3H), 2.50-2.51 (m, 1H), 2.00-2.14 (m, 6H), 1.82 (t, J = 9.6 Hz, 4H), 1.35-1.42 (m, 2H), 1.05-1.12 (m, 2H).
终产物 72	C1		收率: 27.52%. MS (ESI⁺) m/z = 610.23 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.14 (s, 1H), 8.76 (s, 1H), 8.69 (s, 1H), 8.61 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.08 (dd, J = 7.2, 1.2 Hz, 1H), 7.76 (d, J = 7.2 Hz, 1H), 7.43 (s, 1H), 6.99 (s, 1H), 6.56-6.62 (m, 1H), 6.22 (dd, J = 13.6, 0.8 Hz, 1H), 5.74 (d, J = 8.8 Hz, 1H), 4.09 (s, 3H), 3.83 (s, 3H), 2.99 (s, 1H), 2.59 (s,

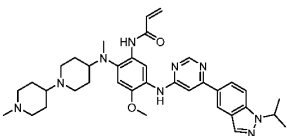
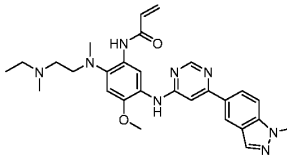
			3H), 2.42 (s, 3H), 2.32-2.40 (m, 5H), 2.16 (brs, 4H), 1.77 (brs, 4H), 1.41 (t, $J = 5.6$ Hz, 2H), 1.25-1.29 (m, 2H).
终产物 73	C2		MS (ESI ⁺) $m/z = 527.17$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.60 (s, 1H), 8.81 (s, 1H), 8.66 (s, 1H), 8.58 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.52 (s, 1H), 7.00 (s, 1H), 6.50-6.55 (m, 1H), 6.22 (dd, $J = 16.5$ Hz, 1H), 5.71 (dd, $J = 11.0$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 2.91 (s, 1H), 2.65 (s, 3H), 2.56 (brs, 1H), 2.11 (s, 4H), 1.99-2.03 (m, 2H), 1.72 (s, 2H), 1.40-1.52 (m, 2H).
终产物 74	C2		收率: 54%. MS (ESI ⁺) $m/z = 513.15$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (s, 1H), 8.82 (s, 1H), 8.65 (s, 1H), 8.63 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.52 (s, 1H), 6.99 (s, 1H), 6.58-6.63 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.75 (d, $J = 11.0$ Hz, 1H), 4.14 (s, 3H), 3.85 (s, 3H), 3.58-3.63 (m, 1H), 2.60-2.70 (s, 1H), 2.59 (s, 3H), 2.50-2.52 (s, 1H), 2.42-2.45 (m, 2H), 2.25 (s, 3H), 1.89-1.97 (m, 1H), 1.73-1.79 (m, 1H).
终产物 75	C24		MS (ESI ⁺) $m/z = 529.17$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.11 (s, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 8.56 (s, 1H), 8.53 (s, 1H), 8.17 (s, 1H), 8.11 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.40 (s, 1H), 7.02 (s, 1H), 6.38-6.44

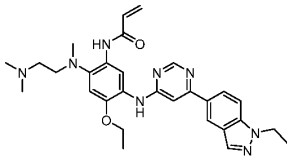
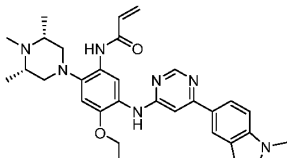
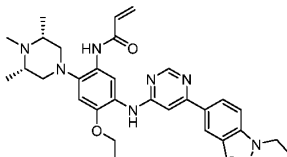
			(m, 1H), 6.26 (dd, $J = 16.5, 1.5$ Hz, 1H), 5.76 (dd, $J = 10.0, 2.0$ Hz, 1H), 4.61 (q, $J = 12.0$ Hz, 1H), 4.09 (s, 3H), 2.88 (s, 2H), 2.71 (s, 3H), 2.33 (brs, 2H), 2.22 (brs, 6H), 1.25 (d, $J = 6.0$ Hz, 6H).
终产物 76	C1		MS (ESI ⁺) $m/z = 529.27$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.92 (s, 1H), 8.61 (s, 1H), 8.50 (d, $J = 0.8$ Hz, 1H), 8.45 (s, 1H), 8.13 (d, $J = 0.8$ Hz, 1H), 8.10 (dd, $J = 8.8, 1.6$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.35 (s, 1H), 6.97 (s, 1H), 6.57- 6.60 (m, 1H), 6.25 (dd, $J = 16.8, 1.6$ Hz, 1H), 5.73 (dd, $J = 10.0, 2.0$ Hz, 1H), 4.08 (s, 3H), 3.87 (s, 3H), 3.46 (brs, 2H), 3.10 (brs, 2H), 2.82-2.92 (m, 3H), 2.72 (s, 3H), 1.95 (s, 3H).
终产物 77	C2		收率: 18%. MS (ESI ⁺) $m/z = 556.22$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.48 (s, 1H), 6.90 (s, 1H), 6.60-6.66 (m, 1H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.5$ Hz, 1H), 4.14 (s, 3H), 3.86 (s, 3H), 2.88 (brs, 4H), 2.62 (brs, 4H), 2.46-2.50 (m, 2H), 2.36-2.40 (m, 2H), 2.17 (s, 6H).
终产物 78	C2		MS (ESI ⁺) $m/z = 556.18$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.36 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.47 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H),

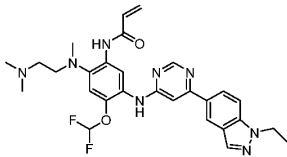
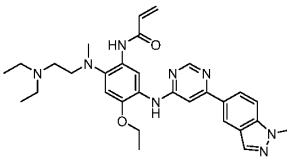
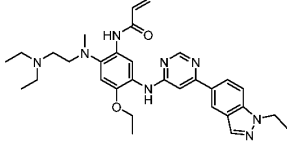
			7.47 (s, 1H), 6.95 (s, 1H), 6.58-6.64 (m, 1H), 6.23 (dd, $J = 18.5, 1.5$ Hz, 1H), 5.75 (d, $J = 10.3$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 2.98 (t, $J = 6.5$ Hz, 2H), 2.49-2.50 (m, 3H), 2.29-2.39 (m, 10H), 2.12 (s, 3H).
终产物 79	C2		收率: 57.6%. MS (ESI ⁺) $m/z = 515.18$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.44 (s, 1H), 8.32 (s, 1H), 8.10 (d, $J = 0.80$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.78 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.46 (s, 1H), 6.91 (s, 1H), 6.61-6.68 (m, 1H), 6.23 (dd, $J = 16.8, 1.6$ Hz, 1H), 5.72 (dd, $J = 12.0, 2.0$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 2.83-2.87 (m, 2H), 2.67 (s, 3H), 2.27 (t, $J = 6.8$ Hz, 2H), 2.13 (s, 6H), 1.61-1.66 (m, 2H).
终产物 80	C2		MS (ESI ⁺) $m/z = 529.16$ [M+H] ⁺ . ¹ H NMR (400M Hz, DMSO- <i>d</i> ₆) δ 9.75 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.61 (s, 1H), 8.33 (s, 1H), 8.10 (d, $J = 0.8$ Hz, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 7.77 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.45 (s, 1H), 6.98 (s, 1H), 6.44-6.51 (m, 1H), 6.24 (d, $J = 16.8$ Hz, 1H), 5.75 (t, $J = 6.4$ Hz, 1H), 4.12 (s, 3H), 3.84 (s, 3H), 2.86 (s, 2H), 2.71 (s, 3H), 2.51-2.53 (m, 6H), 0.95 (t, $J = 6.8$ Hz, 6H).

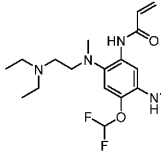
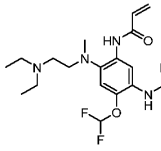
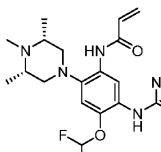
终产物 81	C8		MS (ESI⁺) m/z = 530.09 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.50 (s, 1H), 9.15 (s, 1H), 8.89 (s, 1H), 8.85 (s, 1H), 8.64 (s, 1H), 8.45 (s, 1H), 8.17-8.22 (m, 2H), 7.47 (s, 1H), 6.93 (s, 1H), 6.61-6.67 (m, 1H), 6.24 (dd, J = 17.0, 1.5 Hz, 1H), 5.73 (dd, J = 11.5, 1.5 Hz, 1H), 3.84 (s, 3H), 2.76 (d, J = 10.5 Hz, 2H), 2.69 (t, J = 11.0 Hz, 1H), 2.64 (s, 3H), 2.11 (s, 3H), 1.77 (t, J = 10.5 Hz, 2H), 1.68 (d, J = 11.0 Hz, 2H), 1.55-1.62 (m, 2H).
终产物 82	C8		MS (ESI⁺) m/z = 530.19 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.50 (s, 1H), 9.07 (s, 1H), 8.90 (s, 1H), 8.86 (s, 1H), 8.64 (s, 1H), 8.31 (s, 1H), 8.17-8.21 (m, 2H), 7.42 (s, 1H), 6.85 (s, 1H), 6.58-6.64 (m, 1H), 6.26 (d, J = 17.0 Hz, 1H), 5.75 (d, J = 10.5 Hz, 1H), 3.86 (s, 3H), 2.89 (d, J = 10.5 Hz, 2H), 2.54-2.60 (m, 2H), 2.44 (brs, 2H), 2.24 (s, 3H), 1.04 (d, J = 6.0 Hz, 6H).
终产物 83	C19		MS (ESI⁺) m/z = 555.25 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 8.05 (dd, J = 9.0, 1.5 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.37 (s, 1H), 6.85 (s, 1H), 6.58-6.63 (m, 1H), 6.24 (d, J = 17.0 Hz, 1H), 5.74 (d, J = 10.5 Hz, 1H), 5.01-5.06 (m, 1H), 3.86 (s, 3H), 2.88 (d, J = 10.5 Hz, 2H), 2.54 (t, J = 10.5 Hz, 2H), 2.23-2.45 (m,

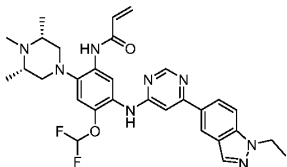
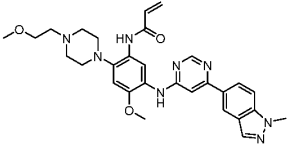
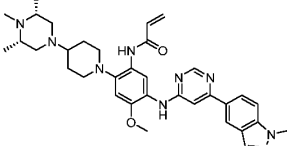
			3H), 1.51 (d, $J = 7.0$ Hz, 6H), 1.04 (t, $J = 6.0$ Hz, 6H).
终产物 84	C19		收率: 24.39%. MS (ESI ⁺) $m/z = 610.29$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.19 (s, 1H), 8.05 (d, $J = 8.5$ Hz, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.35 (s, 1H), 6.85 (s, 1H), 6.65-6.71 (m, 1H), 6.24 (d, $J = 16.5$ Hz, 1H), 5.74 (d, $J = 10.5$ Hz, 1H), 5.01-5.06 (m, 1H), 3.84 (s, 3H), 3.06 (d, $J = 10.5$ Hz, 2H), 2.68 (t, $J = 11.5$ Hz, 2H), 2.53 (brs, 4H), 2.26-2.33 (m, 5H), 2.16 (s, 3H), 1.84 (d, $J = 11.0$ Hz, 2H), 1.68-1.74 (m, 2H), 1.55 (d, $J = 6.0$ Hz, 6H).
终产物 85	C19		MS (ESI ⁺) $m/z = 555.28$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.50 (s, 2H), 8.20 (s, 1H), 8.05 (dd, $J = 9.0, 1.0$ Hz, 1H), 7.82 (d, $J = 9.0$ Hz, 1H), 7.42 (s, 1H), 6.94 (s, 1H), 6.60-6.66 (m, 1H), 6.23 (m, 1H), 5.73 (d, $J = 11.5, 1.5$ Hz, 1H), 5.02-5.06 (m, 1H), 3.85 (s, 3H), 2.77 (d, $J = 9.5$ Hz, 2H), 2.65-2.68 (m, 1H), 2.65 (s, 3H), 2.13 (s, 3H), 1.81 (brs, 2H), 1.69 (d, $J = 10.5$ Hz, 2H), 1.61 (t, $J = 9.0$ Hz, 2H), 1.51 (d, $J = 6.6$ Hz, 6H).
终产物 86	C19		收率: 40%. MS (ESI ⁺) $m/z = 609.32$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.99 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.19 (s, 1H), 8.05 (d, $J = 8.5$ Hz, 1H), 7.81 (d, $J = 9.0$

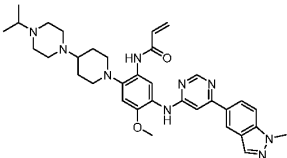
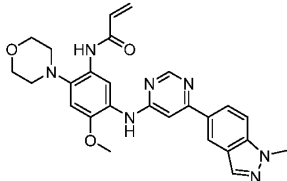
			Hz, 1H), 7.36 (s, 1H), 6.85 (s, 1H), 6.62-6.66 (m, 1H), 6.24 (d, $J = 16.5$ Hz, 1H), 5.74 (d, $J = 10.0$ Hz, 1H), 5.02-5.05 (m, 1H), 3.84 (s, 3H), 3.06 (d, $J = 11.0$ Hz, 2H), 2.83 (d, $J = 9.5$ Hz, 2H), 2.63 (t, $J = 11.5$ Hz, 2H), 2.18 (s, 3H), 1.86 (brs, 2H), 1.76 (d, $J = 11.5$ Hz, 2H), 1.70 (d, $J = 12.5$ Hz, 2H), 1.46-1.51 (m, 8H), 1.16-1.24 (m, 4H).
终产物 87	C19		MS (ESI ⁺) $m/z = 638.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.13 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.52 (s, 1H), 8.50 (s, 1H), 8.19 (s, 1H), 8.05 (d, $J = 7.2$ Hz, 1H), 7.81 (d, $J = 6.8$ Hz, 1H), 7.41 (s, 1H), 6.93 (s, 1H), 6.61-6.66 (m, 1H), 6.23 (d, $J = 13.6$ Hz, 1H), 5.72 (d, $J = 8.8$ Hz, 1H), 5.04 (t, $J = 5.6$ Hz, 1H), 3.84 (s, 3H), 2.85 (d, $J = 8.8$ Hz, 2H), 2.75 (d, $J = 8.8$ Hz, 2H), 2.64-2.68 (m, 1H), 2.63 (s, 3H), 2.10 (brs, 4H), 2.00 (t, $J = 8.8$ Hz, 2H), 1.79 (t, $J = 8.8$ Hz, 2H), 1.70 (d, $J = 8.8$ Hz, 2H), 1.61 (d, $J = 8.8$ Hz, 2H), 1.50 (d, $J = 5.2$ Hz, 8H), 1.36-1.40 (m, 2H).
终产物 88	C1		MS (ESI ⁺) $m/z = 515.23$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.76 (s, 1H), 8.64 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 8.9, 1.1$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.37 (s, 1H), 7.00 (s, 1H), 6.43 (s, 1H), 6.25 (d, $J = 17.0$ Hz, 1H), 5.76 (d, $J = 10.4$ Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H),

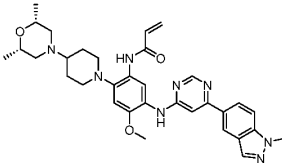
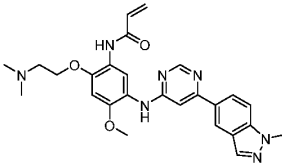
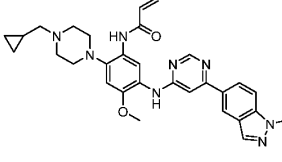
			2.88 (s, 2H), 2.71 (s, 3H), 2.40-2.45 (m, 4H), 2.20 (s, 3H), 1.00 (brs, 3H).
终产物 89	C20		MS (ESI ⁺) m/z = 529.19 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.12 (s, 1H), 8.66 (s, 2H), 8.61 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 8.08 (d, <i>J</i> = 9.0 Hz, 1H), 7.78 (d, <i>J</i> = 9.0 Hz, 1H), 7.37 (s, 1H), 7.01 (s, 1H), 6.37-6.43 (m, 1H), 6.25 (d, <i>J</i> = 17.0 Hz, 1H), 5.76 (d, <i>J</i> = 10.0 Hz, 1H), 4.48 (q, <i>J</i> = 7.5 Hz, 2H), 4.11 (q, <i>J</i> = 6.5 Hz, 2H), 2.87 (t, <i>J</i> = 5.5 Hz, 2H), 2.71 (s, 3H), 2.32 (t, <i>J</i> = 5.5 Hz, 2H), 2.21 (s, 6H), 1.42 (t, <i>J</i> = 7.0 Hz, 3H), 1.30 (t, <i>J</i> = 6.5 Hz, 3H).
终产物 90	C10		MS (ESI ⁺) m/z = 541.25 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 8.09 (d, <i>J</i> = 8.5 Hz, 1H), 7.75 (d, <i>J</i> = 9.0 Hz, 1H), 7.36 (s, 1H), 6.82 (s, 1H), 6.57-6.63 (m, 1H), 6.24 (d, <i>J</i> = 17.0 Hz, 1H), 5.74 (d, <i>J</i> = 10.5 Hz, 1H), 4.12 (q, <i>J</i> = 7.0 Hz, 2H), 4.08 (s, 3H), 2.87 (d, <i>J</i> = 10.5 Hz, 2H), 2.51 (brs, 2H), 2.43 (brs, 2H), 2.23 (s, 3H), 1.31 (t, <i>J</i> = 7.0 Hz, 3H), 1.03 (d, <i>J</i> = 6.5 Hz, 6H).
终产物 91	C20		MS (ESI ⁺) m/z = 555.31 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.31 (s, 1H), 8.18 (s, 1H), 8.08 (dd, <i>J</i> = 9.0, 1.5 Hz, 1H), 7.78 (d, <i>J</i> = 9.0 Hz, 1H), 7.36 (s, 1H), 6.82 (s, 1H), 6.50-6.60

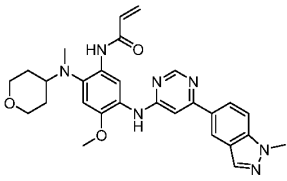
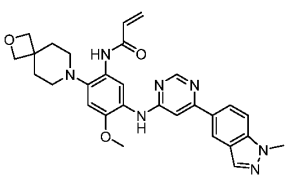
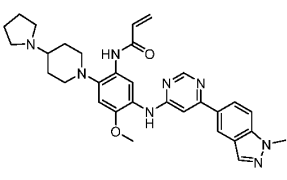
			(m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.7$ Hz, 1H), 4.48 (q, $J = 7.0$ Hz, 2H), 4.12 (q, $J = 7.0$ Hz, 2H), 2.87 (d, $J = 10.0$ Hz, 2H), 2.52 (brs, 2H), 2.48 (brs, 2H), 2.23 (s, 3H), 1.42 (t, $J = 7.5$ Hz, 3H), 1.31 (t, $J = 7.0$ Hz, 3H), 1.02 (d, $J = 6.0$ Hz, 6H).
终产物 92	C25		收率: 6.34%. MS (ESI ⁺) $m/z = 551.16$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.24 (s, 1H), 9.05 (s, 1H), 8.70 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 8.07 (s, 1H), 7.79 (s, 1H), 6.97-7.35 (m, 3H), 6.41 (s, 1H), 6.29 (s, 1H), 5.80 (s, 1H), 4.48 (s, 2H), 2.85 (s, 2H), 2.71 (s, 3H), 2.36 (s, 2H), 2.21 (s, 6H), 1.42 (s, 3H).
终产物 93	C10		MS (ESI ⁺) $m/z = 543.16$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.73 (s, 1H), 8.66 (s, 1H), 8.59 (s, 1H), 8.57 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 8.09 (d, $J = 8.8$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.34 (s, 1H), 6.97 (s, 1H), 6.43-6.50 (m, 1H), 6.25 (dd, $J = 16.2, 1.2$ Hz, 1H), 5.75 (d, $J = 11.6$ Hz, 1H), 4.11 (t, $J = 6.8$ Hz, 2H), 4.08 (s, 3H), 2.85 (t, $J = 5.2$ Hz, 2H), 2.70 (s, 3H), 2.50-2.55 (m, 6H), 1.30 (t, $J = 6.8$ Hz, 3H), 0.95 (t, $J = 6.8$ Hz, 6H).
终产物 94	C20		MS (ESI ⁺) $m/z = 557.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.73-9.89 (m, 1.4H), 8.67 (s, 1H), 8.60-8.62 (m, 1H), 8.51 (s, 1H), 8.37 (s, 0.4H), 8.18 (s, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J =$

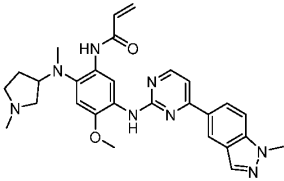
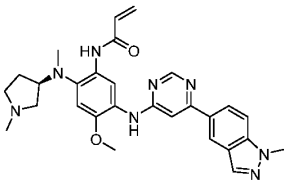
			8.5 Hz, 1H), 7.33-7.45 (m, 1H), 6.97 (s, 1H), 6.91-6.40 (m, 1H), 6.26 (d, $J = 13.5$ Hz, 1H), 5.77 (s, 1H), 4.48 (q, $J = 7.5$ Hz, 2H), 4.10-4.16 (m, 2H), 3.33 (s, 1H), 3.07-3.20 (m, 3H), 2.85 (s, 1H), 2.62-2.70 (m, 3H), 2.51 (s, 3H), 1.42 (t, $J = 7.0$ Hz, 3H), 1.10-1.32 (m, 6H), 0.95 (s, 3H).
终产物 95	C11		收率: 37.23%. MS (ESI ⁺) $m/z = 565.17$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 9.04 (s, 1H), 8.62 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.12-7.33 (m, 3H), 6.46-6.51 (m, 1H), 6.27 (d, $J = 17.0$ Hz, 1H), 5.79 (d, $J = 11.0$ Hz, 1H), 4.08 (s, 3H), 2.84 (s, 2H), 2.71 (s, 3H), 2.52 (s, 6H), 0.96 (t, $J = 7.0$ Hz, 6H).
终产物 96	C25		MS (ESI ⁺) $m/z = 579.06$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 9.05 (s, 1H), 8.62 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.19 (s, 1H), 8.07 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.79 (d, $J = 9.0$ Hz, 1H), 6.97-7.33 (m, 3H), 6.46-6.51 (m, 1H), 6.28 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.79 (dd, $J = 11.5, 1.5$ Hz, 1H), 4.48 (q, $J = 7.0$ Hz, 2H), 2.84 (t, $J = 6.0$ Hz, 2H), 2.71 (s, 3H), 2.51-2.54 (m, 6H), 1.42 (t, $J = 7.0$ Hz, 3H), 0.96 (t, $J = 7.0$ Hz, 6H).
终产物 97	C11		MS (ESI ⁺) $m/z = 563.25$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.17 (s, 1H), 9.03 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.09 (dd, J

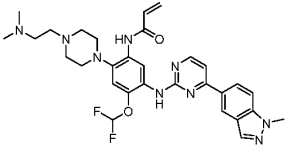
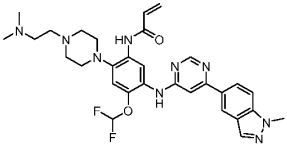
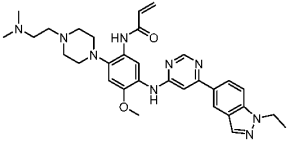
			= 9.0, 1.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.00-7.36 (m, 3H), 6.60-6.66 (m, 1H), 6.26 (dd, J = 17.5, 1.5 Hz, 1H), 5.78 (dd, J = 16.0, 4.5 Hz, 1H), 4.09 (s, 3H), 2.89 (d, J = 7.5 Hz, 2H), 2.45-2.47 (m, 4H), 2.23 (s, 3H), 1.02 (d, J = 5.0 Hz, 6H).
终产物 98	C25		MS (ESI ⁺) m/z = 577.26 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- d_6) δ 9.17 (s, 1H), 9.03 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.19 (s, 1H), 8.07 (dd, J = 8.5, 1.0 Hz, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.00-7.36 (m, 3H), 6.60-6.64 (m, 1H), 6.26 (dd, J = 17.0, 1.5 Hz, 1H), 5.78 (q, J = 11.0 Hz, 1H), 4.48 (q, J = 7.0 Hz, 2H), 2.89 (d, J = 7.5 Hz, 2H), 2.45-2.47 (m, 4H), 2.23 (s, 3H), 1.43 (t, J = 7.0 Hz, 3H), 1.03 (t, J = 6.0 Hz, 6H).
终产物 99	C1		MS (ESI ⁺) m/z = 543.19 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.03 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 6.89 (s, 1H), 6.58-6.65 (m, 1H), 6.23 (d, J = 16.8 Hz, 1H), 5.74 (d, J = 10.8 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 3.48 (t, J = 5.2 Hz, 2H), 3.25 (s, 3H), 2.88 (brs, 4H), 2.64 (brs, 4H), 2.56 (brs, 2H).
终产物 100	C1		MS (ESI ⁺) m/z = 610.27 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.00 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 8.07 (dd, J

			= 8.8, 1.2 Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.36 (s, 1H), 6.84 (s, 1H), 6.65-6.72 (m, 1H), 6.24 (d, $J = 18.0$ Hz, 1H), 5.74 (d, $J = 10.6$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.07 (d, $J = 11.6$ Hz, 2H), 2.80 (brs, 2H), 2.66 (t, $J = 10.8$ Hz, 2H), 1.69-2.41 (m, 12H), 1.00 (brs, 6H).
终产物 101	C1		收率: 28.99%. MS (ESI ⁺) $m/z = 610.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.73 (s, 1H), 8.58 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.16 (s, 1H), 8.07 (d, $J = 9.0$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.36 (s, 1H), 6.85 (s, 1H), 6.64-6.70 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.72-5.74 (d, $J = 10.5$ Hz, 1H), 4.08 (s, 3H), 3.83 (s, 3H), 3.06 (d, $J = 12.5$ Hz, 2H), 2.67 (t, $J = 11.0$ Hz, 2H), 2.56-2.59 (m, 4H), 2.51 (s, 1H), 2.44 (brs, 4H), 2.25 (s, 1H), 1.84 (d, $J = 11.0$ Hz, 2H), 1.71 (q, $J = 10.5$ Hz, 2H), 0.97 (d, $J = 6.0$ Hz, 6H).
终产物 102	C1		MS (ESI ⁺) $m/z = 486.27$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.13 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.40 (s, 1H), 8.17 (s, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.39 (s, 1H), 6.90 (s, 1H), 6.62-6.68 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 14.0$ Hz, 1H), 4.08 (s, 3H), 3.87 (s, 3H), 3.80 (m, 4H), 2.87 (s, 4H).

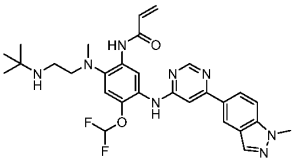
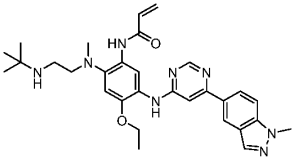
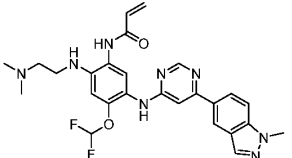
终产物 103	C1		收率: 34%. MS (ESI⁺) m/z = 597.23 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.99 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.07 (d, <i>J</i> = 8.8 Hz, 1H), 7.75 (d, <i>J</i> = 8.8 Hz, 1H), 7.36 (s, 1H), 6.85 (s, 1H), 6.65-6.72 (m, 1H), 6.24 (d, <i>J</i> = 16.8 Hz, 1H), 5.74 (d, <i>J</i> = 10.0 Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.55 (brs, 2H), 3.07 (d, <i>J</i> = 9.2 Hz, 2H), 2.81 (d, <i>J</i> = 10.8 Hz, 2H), 2.67 (t, <i>J</i> = 10.8 Hz, 2H), 2.26 (brs, 1H), 1.70-2.00 (m, 6H), 1.07 (d, <i>J</i> = 5.6 Hz, 3H), 1.03 (d, <i>J</i> = 6.0 Hz, 3H).
终产物 104	C1		MS (ESI⁺) m/z = 488.18 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.68 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.47 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.06 (d, <i>J</i> = 9.0 Hz, 1H), 7.74 (d, <i>J</i> = 8.5 Hz, 1H), 7.28 (s, 1H), 6.94 (s, 1H), 6.45-6.51 (m, 1H), 6.23 (dd, <i>J</i> = 17.0, 1.5 Hz, 1H), 5.74 (dd, <i>J</i> = 11.5, 1.5 Hz, 1H), 4.19 (t, <i>J</i> = 5.5 Hz, 2H), 4.08 (s, 3H), 3.85 (s, 3H), 2.61 (t, <i>J</i> = 5.5 Hz, 2H), 2.27 (s, 6H).
终产物 105	C1		MS (ESI⁺) m/z = 539.26 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.92 (s, 1H), 8.64 (s, 1H), 8.48 (s, 1H), 8.38 (s, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 7.96 (d, <i>J</i> = 9.0 Hz, 1H), 7.64 (d, <i>J</i> = 9.0 Hz, 1H), 7.27 (s, 1H), 6.79 (s, 1H), 6.47-6.53 (m, 1H), 6.12 (d, <i>J</i> = 17.0 Hz, 1H), 5.62 (d, <i>J</i> = 10.0 Hz, 1H), 3.97 (s, 3H), 3.74 (s, 3H), 2.78 (brs, 4H), 2.54 (brs, 4H), 2.15 (d, <i>J</i> =

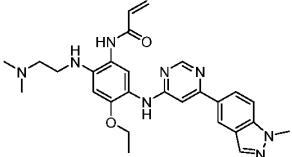
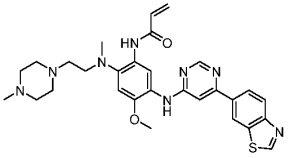
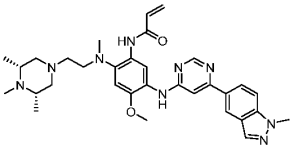
			5.5 Hz, 2H), 0.76 (brs, 1H), 0.37 (d, $J = 7.5$ Hz, 2H), 0.00 (d, $J = 3.5$ Hz, 2H).
终产物 106	C1		MS (ESI ⁺) $m/z = 514.26$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.56 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 9.0, 1.0$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.42 (s, 1H), 6.96 (s, 1H), 6.62-6.68 (m, 1H), 6.25 (dd, $J = 17.0, 1.0$ Hz, 1H), 5.73 (d, $J = 12.0$ Hz, 1H), 4.08 (s, 3H), 3.87 (m, 2H), 3.84 (s, 3H), 3.20 (t, $J = 11.0$ Hz, 2H), 2.92-2.97 (m, 1H), 2.64 (s, 3H), 1.68 (d, $J = 11.0$ Hz, 2H), 1.51-1.60 (m, 2H).
终产物 107	C1		MS (ESI ⁺) $m/z = 526.27$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 8.9, 1.1$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.37 (s, 1H), 6.84 (s, 1H), 6.61-6.67 (m, 1H), 6.24 (d, $J = 16.9$ Hz, 1H), 5.73 (d, $J = 10.6$ Hz, 1H), 4.38 (s, 4H), 4.08 (s, 3H), 3.84 (s, 3H), 2.75 (brs, 4H), 1.99 (brs, 4H).
终产物 108	C1		收率: 31.58%. MS (ESI ⁺) $m/z = 553.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.36 (s, 1H), 6.86 (s, 1H), 6.62-6.68 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.73 (d, $J = 11.0$ Hz, 1H),

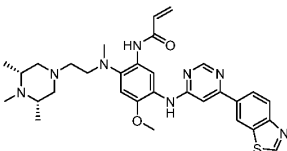
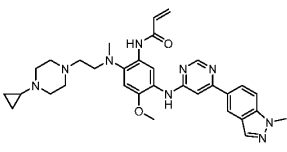
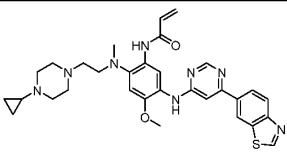
			4.08 (s, 3H), 3.84 (s, 3H), 3.03 (d, $J = 10.5$ Hz, 2H), 2.69 (t, $J = 11.0$ Hz, 2H), 2.57 (brs, 4H), 2.09 (brs, 1H), 1.93 (brs, 2H), 1.70 (s, 6H).
终产物 109	C3		MS (ESI ⁺) $m/z = 513.39$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.37 (s, 1H), 9.22 (s, 1H), 8.93 (s, 1H), 8.49 (d, $J = 5.0$ Hz, 1H), 8.31 (d, $J = 9.0$ Hz, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.72 (d, $J = 9.0$ Hz, 1H), 7.50 (d, $J = 5.0$ Hz, 1H), 7.00 (s, 1H), 6.61-6.67 (m, 1H), 6.34 (d, $J = 17.0$ Hz, 1H), 5.81 (d, $J = 10.5$ Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.32-3.59 (m, 1H), 2.51-2.58 (m, 4H), 2.47-2.50 (m, 1H), 2.38-2.43 (m, 2H), 2.22 (s, 3H), 1.89-1.93 (m, 1H), 1.71-1.75 (m, 1H).
终产物 110	C1		MS (ESI ⁺) $m/z = 513.27$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.32 (s, 1H), 8.74 (s, 1H), 8.62 (s, 1H), 8.61 (s, 1H), 8.50 (s, 1H), 8.17 (d, $J = 0.8$ Hz, 1H), 8.08 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 1H), 7.42 (s, 1H), 6.97 (s, 1H), 6.55-6.63 (m, 1H), 6.24 (dd, $J = 17.2, 2.0$ Hz, 1H), 5.74 (dd, $J = 10.4, 1.6$ Hz, 1H), 4.09 (s, 3H), 3.84 (s, 3H), 3.50-3.70 (m, 1H), 2.58 (s, 3H), 2.55-2.57 (m, 1H), 2.49-2.50 (m, 1H), 2.40-2.47 (m, 2H), 2.22 (s, 3H), 1.90-1.93 (m, 1H), 1.73-1.75 (m, 1H).

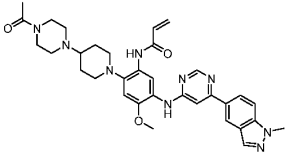
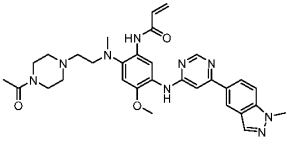
			4H), 2.62 (s, 4H), 2.47 (t, $J = 6.5$ Hz, 2H), 2.38 (t, $J = 6.5$ Hz, 2H), 2.16 (s, 6H).
终产物 114	C27		MS (ESI ⁺) $m/z = 592.11$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.77 (s, 2H), 8.46-8.48 (m, 2H), 8.25 (dd, $J = 8.9, 1.2$ Hz, 1H), 8.15 (s, 1H), 7.72 (d, $J = 8.9$ Hz, 1H), 7.49 (d, $J = 5.3$ Hz, 1H), 7.00-7.29 (m, 2H), 6.66-6.72 (m, 1H), 6.31 (dd, $J = 17.0, 1.4$ Hz, 1H), 5.81 (d, $J = 11.3$ Hz, 1H), 4.09 (s, 3H), 2.84 (t, $J = 4.3$ Hz, 4H), 2.63 (s, 4H), 2.47 (d, $J = 7.6$ Hz, 2H), 2.37 (d, $J = 6.0$ Hz, 2H), 2.16 (s, 6H).
终产物 115	C11		MS (ESI ⁺) $m/z = 592.30$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 9.04 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.09 (dd, $J = 10.0, 1.0$ Hz, 1H), 7.76 (d, $J = 8.9$ Hz, 1H), 7.37 (s, 1H), 7.00-7.30 (m, 2H), 6.62-6.68 (m, 1H), 6.26 (d, $J = 17.0$ Hz, 1H), 5.78 (d, $J = 11.0$ Hz, 1H), 4.09 (s, 3H), 2.84 (d, $J = 4.5$ Hz, 4H), 2.63 (brs, 4H), 2.44-2.49 (m, 2H), 2.37 (t, $J = 7.5$ Hz, 2H), 2.16 (s, 6H).
终产物 116	C26		MS (ESI ⁺) $m/z = 570.33$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.76 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.18 (s, 1H), 8.06 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.38 (s, 1H), 6.89 (s, 1H), 6.59-6.64 (m, 1H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.0$ Hz, 1H), 4.48 (d, $J = 6.5$ Hz, 2H),

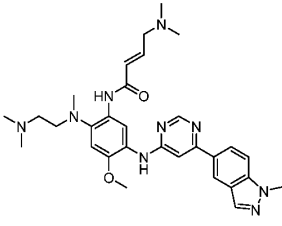
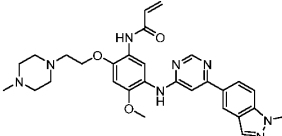
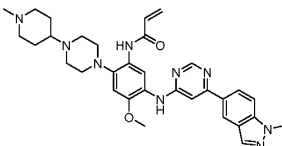
			3.85 (s, 3H), 2.87 (brs, 4H), 2.62 (brs, 4H), 2.46-2.50 (m, 2H), 2.37 (brs, 2H), 2.16 (s, 6H), 1.42 (t, $J = 6.0$ Hz, 3H).
终产物 117	C10		MS (ESI ⁺) $m/z = 570.19$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 8.09 (dd, $J = 8.9, 1.3$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.37 (s, 1H), 6.87 (s, 1H), 6.59-6.64 (m, 1H), 6.23 (d, $J = 18.1$ Hz, 1H), 5.74 (d, $J = 10.9$ Hz, 1H), 4.12 (q, $J = 9.0$ Hz, 2H), 4.08 (s, 3H), 2.85 (t, $J = 4.3$ Hz, 4H), 2.61 (brs, 4H), 2.45-2.49 (m, 2H), 2.37 (t, $J = 6.8$ Hz, 2H), 2.16 (s, 6H), 1.31 (t, $J = 6.9$ Hz, 3H)
终产物 118	C26		MS (ESI ⁺) $m/z = 570.31$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.33 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 8.47 (s, 1H), 8.18 (s, 1H), 8.06 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.38 (s, 1H), 6.96 (s, 1H), 6.57-6.64 (m, 1H), 6.25 (d, $J = 16.9$ Hz, 1H), 5.74 (d, $J = 9.6$ Hz, 1H), 4.48 (q, $J = 7.2$ Hz, 2H), 3.85 (s, 3H), 2.98 (t, $J = 6.2$ Hz, 2H), 2.70 (s, 3H), 2.30-2.38 (m, 10H), 2.13 (s, 3H), 1.42 (t, $J = 7.2$ Hz, 3H).
终产物 119	C10		MS (ESI ⁺) $m/z = 570.23$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (s, 1H), 8.65 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.45 (s, 1H), 8.17 (s, 1H), 8.10 (dd, $J = 9.0, 1.0$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.38 (s, 1H), 6.96 (s, 1H), 6.59-6.65

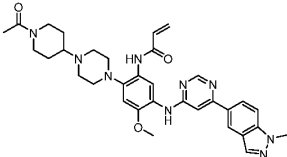
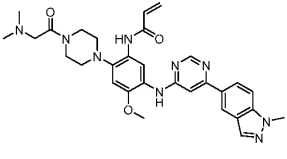
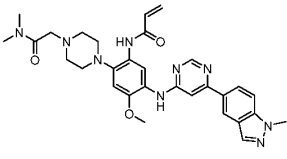
			(m, 1H), 6.25 (dd, $J = 18.0, 1.0$ Hz, 1H), 5.76 (d, $J = 9.0$ Hz, 1H), 4.11-4.14 (m, 2H), 4.09 (s, 3H), 2.98 (t, $J = 6.0$ Hz, 2H), 2.69 (s, 3H), 2.36-2.50 (m, 10H), 2.15 (s, 3H), 1.32 (t, $J = 7.0$ Hz, 3H).
终产物 120	C11		MS (ESI ⁺) $m/z = 565.12$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 9.05 (s, 1H), 8.60 (s, 1H), 8.58 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.09 (dd, $J = 8.9, 1.4$ Hz, 1H), 7.76 (d, $J = 8.9$ Hz, 1H), 7.33 (s, 1H), 6.99-7.29 (m, 2H), 6.66-6.72 (m, 1H), 6.28 (dd, $J = 17.0, 1.6$ Hz, 1H), 5.77 (dd, $J = 10.3, 1.5$ Hz, 1H), 4.09 (s, 3H), 3.31 (s, 1H), 2.87 (t, $J = 5.7$ Hz, 2H), 2.60-2.70 (m, 5H), 1.04 (d, $J = 8.5$ Hz, 9H).
终产物 121	C10		MS (ESI ⁺) $m/z = 543.10$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.45 (s, 1H), 8.66 (s, 1H), 8.60 (s, 1H), 8.54 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 8.08 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.33 (s, 1H), 6.93 (s, 1H), 6.63-6.68 (m, 1H), 6.24 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.71 (dd, $J = 11.5, 1.5$ Hz, 1H), 4.10-4.12 (m, 2H), 4.08 (s, 3H), 2.88 (t, $J = 5.5$ Hz, 2H), 2.67 (s, 3H), 2.55-2.61 (m, 2H), 1.60 (s, 1H), 1.30 (t, $J = 7.0$ Hz, 3H), 1.03 (s, 9H).
终产物 122	C11		MS (ESI ⁺) $m/z = 523.29$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.76 (s, 1H), 8.85 (s, 1H), 8.54 (s, 1H), 8.47 (s, 1H), 8.16 (s, 1H), 8.06 (d, $J = 8.0$ Hz,

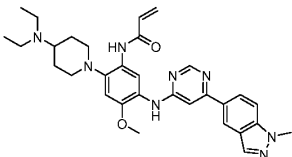
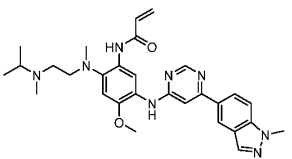
			1H), 7.73 (d, $J = 7.5$ Hz, 1H), 7.53 (s, 1H), 6.98-7.28 (m, 2H), 6.49-6.54 (m, 2H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 9.5$ Hz, 1H), 5.31 (s, 1H), 4.08 (s, 3H), 3.12 (brs, 2H), 3.07(brs, 2H), 2.20 (s, 6H).
终产物 123	C10		MS (ESI ⁺) $m/z = 501.09$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.41 (s, 1H), 8.54 (s, 1H), 8.52 (s, 1H), 8.46 (s, 1H), 8.15 (s, 1H), 8.06 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.46 (s, 1H), 7.13 (s, 1H), 6.44-6.50 (m, 1H), 6.40 (s, 1H), 6.22 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.72 (dd, $J = 10.0, 1.5$ Hz, 1H), 4.88 (brs, 1H), 4.09-4.12 (m, 2H), 4.07 (s, 3H), 3.07-3.18 (m, 2H), 2.19-2.49 (m, 2H), 2.19 (s, 6H), 1.27 (t, $J = 6.5$ Hz, 3H).
终产物 124	C8		MS (ESI ⁺) $m/z = 559.40$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.49 (s, 1H), 9.35 (s, 1H), 8.89 (s, 1H), 8.85 (s, 1H), 8.64 (s, 1H), 8.42 (s, 1H), 8.16-8.21 (m, 2H), 7.43 (s, 1H), 6.96 (s, 1H), 6.59-6.65 (m, 1H), 6.26 (d, $J = 16.8$ Hz, 1H), 5.75 (dd, $J = 10.5, 6.0$ Hz, 1H), 3.85 (s, 3H), 2.99 (s, 2H), 2.71 (s, 3H), 2.36-2.50 (m, 10H), 2.16 (s, 3H).
终产物 125	C1		MS (ESI ⁺) $m/z = 584.30$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.39 (s, 1H), 6.96 (s, 1H), 6.57-6.63

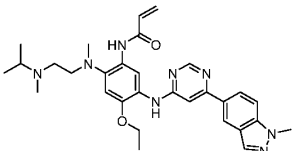
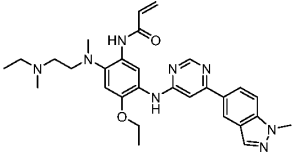
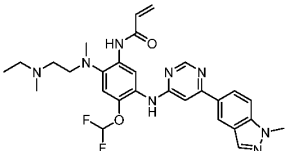
			(m, 1H), 6.25 (dd, $J = 18.5, 1.5$ Hz, 1H), 5.74 (d, $J = 11.0$ Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 2.97 (t, $J = 6.5$ Hz, 2H), 2.70 (s, 3H), 2.67 (d, $J = 10.5$ Hz, 2H), 2.32 (brs, 2H), 2.09-2.11 (m, 5H), 1.69 (t, $J = 10.5$ Hz, 2H), 0.92 (d, $J = 5.5$ Hz, 6H).
终产物 126	C8		MS (ESI ⁺) $m/z = 587.46$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.49 (s, 1H), 9.35 (s, 1H), 8.90 (s, 1H), 8.84 (s, 1H), 8.64 (s, 1H), 8.42 (s, 1H), 8.16-8.21 (m, 2H), 7.44 (s, 1H), 6.96 (s, 1H), 6.57-6.64 (m, 1H), 6.27 (dd, $J = 16.8, 1.2$ Hz, 1H), 5.75 (d, $J = 11.6$ Hz, 1H), 3.85 (s, 3H), 2.97 (t, $J = 6.0$ Hz, 2H), 2.71 (s, 3H), 2.66 (d, $J = 10.4$ Hz, 2H), 2.33 (brs, 2H), 2.10 (s, 5H), 1.70 (t, $J = 10.0$ Hz, 2H), 0.92 (d, $J = 5.2$ Hz, 6H).
终产物 127	C1		MS (ESI ⁺) $m/z = 582.46$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.35 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 8.07 (d, $J = 10.0, 1.0$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.38 (s, 1H), 6.97 (s, 1H), 6.61-6.65 (m, 1H), 6.25 (d, $J = 17.0$ Hz, 1H), 5.76 (d, $J = 10.5$ Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 2.98 (t, $J = 6.5$ Hz, 2H), 2.70 (s, 3H), 2.45 (brs, 4H), 2.31-2.37 (m, 6H), 1.55 (brs, 1H), 0.36 (d, $J = 4.5$ Hz, 2H), 0.24 (s, 2H).
终产物 128	C8		MS (ESI ⁺) $m/z = 585.26$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.49 (s, 1H), 9.36 (s, 1H), 8.89 (s, 1H), 8.85 (s,

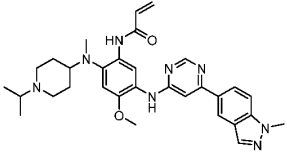
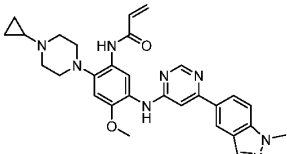
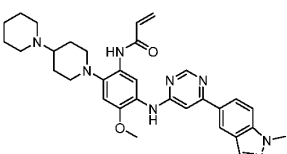
			1H), 8.64 (s, 1H), 8.43 (s, 1H), 8.16-8.21 (m, 2H), 7.43 (s, 1H), 6.97 (s, 1H), 6.60-6.65 (m, 1H), 6.27 (d, $J = 17.0$ Hz, 1H), 5.76 (d, $J = 11.0$ Hz, 1H), 3.85 (s, 3H), 2.98 (t, $J = 6.5$ Hz, 2H), 2.71 (s, 3H), 2.47 (brs, 4H), 2.37 (t, $J = 6.5$ Hz, 3H), 2.31 (brs, 3H), 1.51-1.55 (m, 1H), 0.36 (d, $J = 4.5$ Hz, 2H), 0.23 (d, $J = 2.5$ Hz, 2H).
终产物 129	C1		收率: 30.39%. MS (ESI ⁺) $m/z = 610.35$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.07 (d, $J = 9.0$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.36 (s, 1H), 6.84 (s, 1H), 6.64-6.70 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.73 (d, $J = 10.0$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.43 (brs, 4H), 3.07 (d, $J = 10.0$ Hz, 2H), 2.68 (t, $J = 11.0$ Hz, 2H), 2.53 (brs, 2H), 2.50 (s, 2H), 2.36 (brs, 1H), 1.99 (s, 3H), 1.83 (d, $J = 10.5$ Hz, 2H), 1.73 (d, $J = 10.5$ Hz, 2H).
终产物 130	C1		MS (ESI ⁺) $m/z = 584.31$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.31 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.45 (s, 1H), 8.17 (s, 1H), 8.07 (d, $J = 9.0$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.38 (s, 1H), 6.96 (s, 1H), 6.57-6.63 (m, 1H), 6.26 (d, $J = 17.5$ Hz, 1H), 5.76 (d, $J = 10.0$ Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 3.36-3.38 (m, 4H), 3.01 (t, $J = 6.5$ Hz, 2H), 2.72 (s, 3H), 2.42 (t, $J = 6.5$ Hz, 2H),

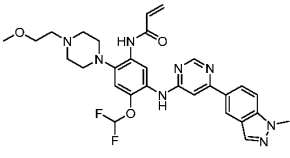
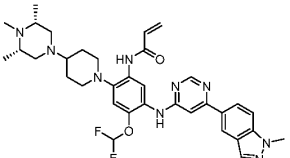
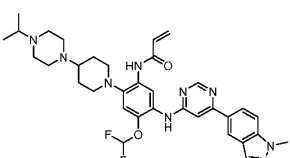
			2.34 (brs, 2H), 2.29 (brs, 2H), 1.95 (s, 3H).
终产物 131	C1		MS (ESI ⁺) m/z = 558.29 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.05 (s, 1H), 8.75 (s, 1H), 8.71 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.07 (dd, <i>J</i> = 8.5, 1.0 Hz, 1H), 7.75 (d, <i>J</i> = 9.0 Hz, 1H), 7.37 (s, 1H), 7.02 (s, 1H), 6.69-6.76 (m, 1H), 6.21 (d, <i>J</i> = 15.5 Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.07 (d, <i>J</i> = 6.0 Hz, 2H), 2.85 (t, <i>J</i> = 5.0 Hz, 2H), 2.72 (s, 3H), 2.35 (t, <i>J</i> = 5.5 Hz, 2H), 2.23 (s, 6H), 2.18 (s, 6H).
终产物 132	C1		MS (ESI ⁺) m/z = 543.26 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.21 (s, 1H), 8.73 (s, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 8.24 (s, 1H), 8.16 (s, 1H), 8.06 (dd, <i>J</i> = 9.0, 1.5 Hz, 1H), 7.74 (d, <i>J</i> = 9.0 Hz, 1H), 7.25 (s, 1H), 6.91 (s, 1H), 6.56-6.61 (m, 1H), 6.22 (dd, <i>J</i> = 17.0, 1.5 Hz, 1H), 5.72 (dd, <i>J</i> = 11.5, 1.5 Hz, 1H), 4.21 (t, <i>J</i> = 5.5 Hz, 2H), 4.08 (s, 3H), 3.85 (s, 3H), 2.72 (t, <i>J</i> = 5.5 Hz, 2H), 2.51 (brs, 4H), 2.30 (brs, 4H), 2.15 (s, 3H).
终产物 133	C1		MS (ESI ⁺) m/z = 582.30 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 8.18 (s, 1H), 8.09 (d, <i>J</i> = 9.0 Hz, 1H), 7.77 (d, <i>J</i> = 9.0 Hz, 1H), 7.39 (s, 1H), 6.90 (s, 1H), 6.60-6.65 (m, 1H), 6.25 (d, <i>J</i> = 17.0 Hz, 1H), 5.75 (d, <i>J</i> = 10.5 Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H),

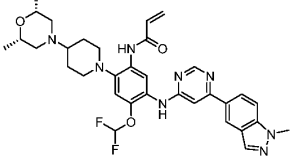
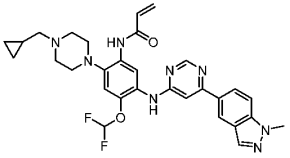
			2.88 (s, 4H), 2.81 (d, $J = 10.5$ Hz, 2H), 2.69 (s, 4H), 2.14-2.21 (m, 1H), 2.08 (s, 3H), 1.861 (t, $J = 11.5$ Hz, 2H), 1.775 (d, $J = 11.0$ Hz, 2H), 1.46 (q, $J = 10.5$ Hz, 2H).
终产物 134	C1		MS (ESI ⁺) $m/z = 610.35$ [M+H] ⁺ . ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 8.18 (s, 1H), 8.08 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.76 (d, $J = 8.7$ Hz, 1H), 7.39 (s, 1H), 6.89 (s, 1H), 6.58-6.67 (m, 1H), 6.24 (dd, $J = 16.8, 1.5$ Hz, 1H), 5.74 (d, $J = 10.8$ Hz, 1H), 4.39 (d, $J = 12.6$ Hz, 1H), 4.09 (s, 3H), 3.86 (s, 4H), 3.01 (d, $J = 11.4$ Hz, 1H), 2.89 (s, 4H), 2.71 (s, 4H), 2.51-2.60 (m, 1H), 2.01 (s, 3H), 1.70-1.90 (m, 2H), 1.24-1.43 (m, 3H).
终产物 135	C1		MS (ESI ⁺) $m/z = 570.30$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.13 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.45 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 8.9, 1.2$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.40 (s, 1H), 6.89 (s, 1H), 6.65-6.71 (m, 1H), 6.26 (d, $J = 16.9$ Hz, 1H), 5.75 (d, $J = 10.9$ Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 3.75 (brs, 2H), 3.67 (brs, 2H), 3.12 (s, 2H), 2.83-2.86 (m, 4H), 2.21 (s, 6H).
终产物 136	C1		MS (ESI ⁺) $m/z = 570.32$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.76 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.08 (dd, J

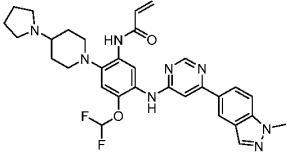
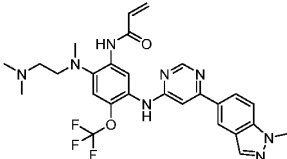
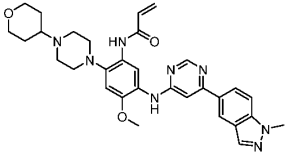
			= 8.5, 1.0 Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.39 (s, 1H), 6.89 (s, 1H), 6.59-6.65 (m, 1H), 6.24 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.74 (d, $J = 11.0$ Hz, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 3.21 (s, 2H), 3.08 (s, 3H), 2.90 (brs, 4H), 2.83 (s, 3H), 2.67 (brs, 4H).
终产物 137	C1		MS (ESI ⁺) $m/z = 555.38$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 10.0, 1.0$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.36 (s, 1H), 6.86 (s, 1H), 6.66-6.71 (m, 1H), 6.24 (d, $J = 16.5$ Hz, 1H), 5.74 (d, $J = 11.0$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.05 (d, $J = 11.0$ Hz, 2H), 2.66-2.71 (m, 2H), 2.53-2.60 (m, 5H), 1.74 (d, $J = 2.5$ Hz, 4H), 1.03 (d, $J = 6.0$ Hz, 2H), 0.99 (d, $J = 7.0$ Hz, 4H).
终产物 138	C1		MS (ESI ⁺) $m/z = 529.28$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.83 (s, 1H), 8.82 (s, 1H), 8.68 (s, 1H), 8.64 (s, 1H), 8.40 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.78 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.44 (s, 1H), 6.99 (s, 1H), 6.40-6.46 (m, 1H), 6.27 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.77 (dd, $J = 11.5, 1.5$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 2.81-2.88 (m, 3H), 2.73 (s, 3H), 2.43-2.46 (m, 2H), 2.20 (s, 3H), 0.97 (d, $J = 6.5$ Hz, 6H).

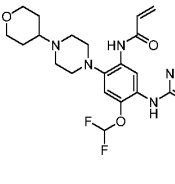
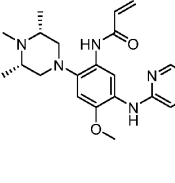
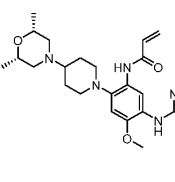
终产物 139	C10		MS (ESI ⁺) m/z = 543.22 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.81 (s, 1H), 8.67 (s, 1H), 8.64 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.09 (dd, J = 8.9, 1.4 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.33 (s, 1H), 6.98 (s, 1H), 6.40-6.43 (m, 1H), 6.26 (dd, J = 16.9, 1.7 Hz, 1H), 5.76 (dd, J = 11.5, 1.5 Hz, 1H), 4.10-4.13 (m, 2H), 4.09 (s, 3H), 2.80-2.86 (m, 3H), 2.72 (s, 3H), 2.44 (t, J = 6.0 Hz, 2H), 2.20 (s, 3H), 1.30 (t, J = 6.9 Hz, 3H), 0.98 (d, J = 6.5 Hz, 6H).
终产物 140	C10		MS (ESI ⁺) m/z = 529.21 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.67 (s, 1H), 8.61 (s, 2H), 8.52 (s, 1H), 8.17 (s, 1H), 8.10 (dd, J = 8.9, 1.5 Hz, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.37 (s, 1H), 6.99 (s, 1H), 6.44 (brs, 1H), 6.26 (d, J = 16.7 Hz, 1H), 5.76 (d, J = 10.9 Hz, 1H), 4.09-4.12 (m, 5H), 2.88 (brs, 2H), 2.70 (brs, 3H), 2.41-2.45 (m, 4H), 2.10-2.30 (m, 3H), 1.31 (t, J = 6.6 Hz, 3H), 1.06 (brs, 3H).
终产物 141	C11		MS (ESI ⁺) m/z = 551.21 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.04 (s, 1H), 9.05 (s, 1H), 8.67 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 8.09 (s, 1H), 7.77 (s, 1H), 7.23 (s, 1H), 6.98-7.28 (m, 2H), 6.45 (s, 1H), 6.29 (d, J = 15.0 Hz, 1H), 5.81 (s, 1H), 4.09 (s, 3H), 2.86 (s, 2H), 2.72 (s, 3H), 2.49 (brs, 4H), 2.20 (s, 3H), 1.01 (s, 3H).

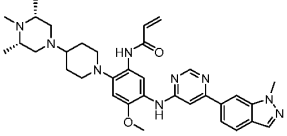
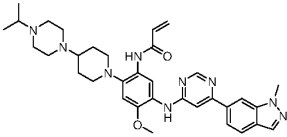
终产物 142	C1		MS (ESI ⁺) m/z = 555.28 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.13 (s, 1H), 8.75 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.09 (dd, J = 9.0, 1.5 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.42 (s, 1H), 6.94 (s, 1H), 6.61-6.69 (m, 1H), 6.26 (dd, J = 17.0, 1.0 Hz, 1H), 5.74 (d, J = 11.0 Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 2.78 (s, 2H), 2.64-2.70 (m, 5H), 1.90-2.10 (m, 2H), 1.71-1.80 (m, 2H), 1.52-1.54 (m, 2H), 0.93 (brs, 6H).
终产物 143	C1		MS (ESI ⁺) m/z = 525.30 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.38 (s, 1H), 8.18 (s, 1H), 8.08 (dd, J = 9.0, 1.5 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 6.89 (s, 1H), 6.61-6.67 (m, 1H), 6.25 (dd, J = 17.5, 1.5 Hz, 1H), 5.75 (d, J = 11.0 Hz, 1H), 4.09 (s, 3H), 3.84 (s, 3H), 2.83 (d, J = 4.5 Hz, 4H), 2.76 (brs, 4H), 1.72 (q, J = 3.0 Hz, 1H), 0.45-0.47 (m, 2H), 0.32-0.34 (m, 2H).
终产物 144	C1		MS (ESI ⁺) m/z = 567.31 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.08 (dd, J = 8.9, 1.4 Hz, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.37 (s, 1H), 6.85 (s, 1H), 6.65-6.70 (m, 1H), 6.25 (d, J = 17.1 Hz, 1H), 5.75 (d, J = 10.7 Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 2.64-2.70 (m, 2H), 2.40-2.49 (m, 4H), 2.33-2.37 (m, 1H), 1.79 (brs, 4H),

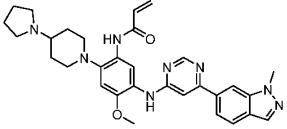
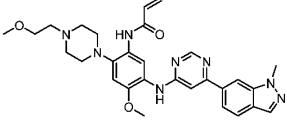
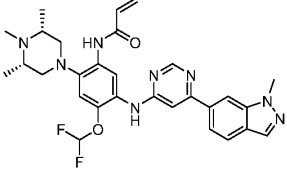
			1.41-1.51 (m, 4H), 1.11 (s, 4H).
终产物 145	C11		MS (ESI ⁺) m/z = 579.30 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 9.05 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.10 (dd, J = 9.0, 1.5 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.37 (s, 1H), 7.01-7.31 (m, 2H), 6.63-6.69 (m, 1H), 6.27 (dd, J = 17.0, 1.5 Hz, 1H), 5.78 (d, J = 11.5 Hz, 1H), 4.09 (s, 3H), 3.48 (t, J = 5.5 Hz, 2H), 3.26 (s, 3H), 2.85 (d, J = 4.0 Hz, 4H), 2.65 (s, 4H), 2.57 (t, J = 5.5 Hz, 2H).
终产物 146	C11		MS (ESI ⁺) m/z = 646.30 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.11 (s, 1H), 9.03 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 6.95-7.32 (m, 2H), 6.69-6.76 (m, 1H), 6.25 (dd, J = 18.4, 1.6 Hz, 1H), 5.78 (d, J = 11.6 Hz, 1H), 4.09 (s, 3H), 3.07 (d, J = 10.8 Hz, 2H), 2.78 (d, J = 10.4 Hz, 2H), 2.61 (t, J = 11.2 Hz, 2H), 2.22-2.23 (m, 1H), 2.09-2.14 (m, 5H), 1.93 (t, J = 10.4 Hz, 2H), 1.84 (d, J = 10.8 Hz, 2H), 1.70-1.76 (m, 2H), 0.99 (d, J = 6.0 Hz, 6H).
终产物 147	C11		MS (ESI ⁺) m/z = 646.36 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 9.01 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 8.08 (dd, J = 8.8, 1.2 Hz, 1H), 7.75 (d, J = 8.8 Hz,

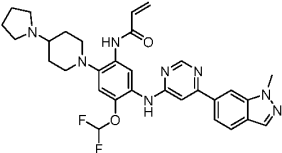
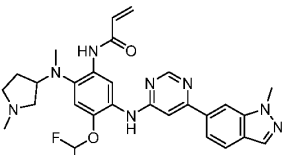
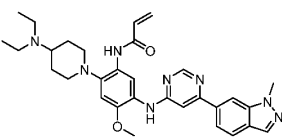
			1H), 7.35 (s, 1H), 7.00-7.31 (m, 2H), 6.66-6.73 (m, 1H), 6.27 (d, $J = 17.2$ Hz, 1H), 5.77 (d, $J = 11.6$ Hz, 1H), 4.08 (s, 3H), 3.07 (d, $J = 8.8$ Hz, 2H), 2.51-2.66 (m, 7H), 2.45 (brs, 4H), 2.27 (brs, 1H), 1.84 (d, $J = 11.6$ Hz, 2H), 1.68-1.73 (m, 2H), 0.97 (d, $J = 3.6$ Hz, 6H).
终产物 148	C11		MS (ESI ⁺) $m/z = 633.25$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.11 (s, 1H), 9.04 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.09 (d, $J = 9.2$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 1H), 7.35 (s, 1H), 6.95-7.32 (m, 2H), 6.68-6.75 (m, 1H), 6.27 (d, $J = 16.8$ Hz, 1H), 5.78 (d, $J = 10.4$ Hz, 1H), 4.09 (s, 3H), 3.55 (s, 2H), 3.07 (d, $J = 10.8$ Hz, 2H), 2.81 (d, $J = 10.4$ Hz, 2H), 2.63 (t, $J = 11.7$ Hz, 2H), 2.27-2.31 (m, 1H), 1.65-1.83 (m, 6H), 1.07 (d, $J = 6.0$ Hz, 6H).
终产物 149	C11		MS (ESI ⁺) $m/z = 575.27$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 9.04 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.09 (d, $J = 9.0$ Hz, 1H), 7.76 (d, $J = 9.2$ Hz, 1H), 7.37 (s, 1H), 6.96-7.33 (m, 2H), 6.61-6.67 (m, 1H), 6.26 (d, $J = 17.1$ Hz, 1H), 5.78 (d, $J = 10.1$ Hz, 1H), 4.09 (s, 3H), 2.87 (s, 4H), 2.67 (s, 4H), 2.27 (d, $J = 6.0$ Hz, 2H), 0.87 (brs, 1H), 0.49 (d, $J = 6.6$ Hz, 2H), 0.11 (d, $J = 3.6$ Hz, 2H).

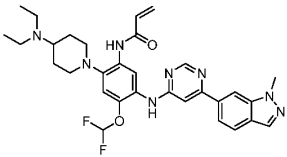
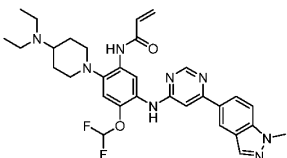
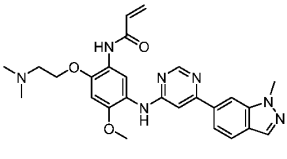
终产物 150	C11		MS (ESI ⁺) m/z = 589.26 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.12 (s, 1H), 9.03 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.38 (s, 1H), 8.18 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.35 (s, 1H), 6.95-7.14 (m, 2H), 6.65-6.72 (m, 1H), 6.26 (d, J = 16.8 Hz, 1H), 5.78 (d, J = 10.4 Hz, 1H), 4.09 (s, 3H), 3.03 (d, J = 10.6 Hz, 2H), 2.66 (t, J = 11.2 Hz, 2H), 2.54 (brs, 4H), 2.12 (brs, 1H), 1.95 (d, J = 10.0 Hz, 2H), 1.70 (s, 6H).
终产物 151	C14		MS (ESI ⁺) m/z = 555.25 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.31 (s, 1H), 9.27 (s, 1H), 8.80 (s, 1H), 8.63 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H), 8.09 (dd, J = 8.9, 1.3 Hz, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.39 (s, 1H), 7.32 (s, 1H), 6.41-6.47 (m, 1H), 6.30 (dd, J = 16.9, 1.7 Hz, 1H), 5.83 (dd, J = 10.1, 1.7 Hz, 1H), 4.10 (s, 3H), 2.87 (t, J = 5.5 Hz, 2H), 2.72 (s, 3H), 2.37 (t, J = 5.1 Hz, 2H), 2.23 (s, 6H).
终产物 152	C1		MS (ESI ⁺) m/z = 569.28 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.73 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 6.89 (s, 1H), 6.58-6.65 (m, 1H), 6.23 (d, J = 16.8 Hz, 1H), 5.73 (d, J = 10.4 Hz, 1H), 4.08 (s, 3H), 3.90-3.92 (m, 2H), 3.85 (s, 3H), 3.27-3.33 (m, 2H), 2.88 (brs, 4H), 2.70 (brs, 4H), 2.41-2.45 (m, 1H), 1.73-1.77 (m, 2H), 1.39-1.48 (m, 1H).

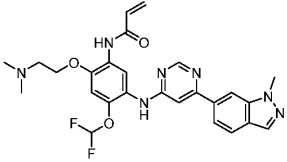
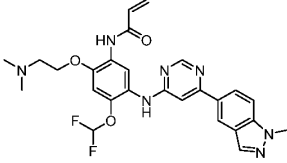
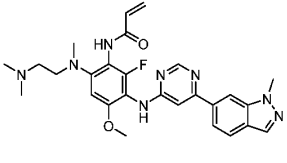
			2H).
终产物 153	C11		MS (ESI ⁺) m/z = 605.35 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.16 (s, 1H), 9.04 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.09 (dd, <i>J</i> = 9.2, 1.6 Hz, 1H), 7.76 (d, <i>J</i> = 8.8 Hz, 1H), 7.37 (s, 1H), 6.97-7.34 (m, 2H), 6.62-6.69 (m, 1H), 6.26 (d, <i>J</i> = 16.9 Hz, 1H), 5.77 (d, <i>J</i> = 11.6 Hz, 1H), 4.09 (s, 3H), 3.91 (d, <i>J</i> = 6.8 Hz, 2H), 3.27-3.32 (m, 2H), 2.86 (brs, 4H), 2.71 (brs, 4H), 2.44-2.50 (m, 1H), 1.75 (d, <i>J</i> = 13.0 Hz, 2H), 1.41-1.48 (m, 2H).
终产物 154	C2		MS (ESI ⁺) m/z = 527.36 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.06 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.87 (d, <i>J</i> = 8.5 Hz, 1H), 7.77 (d, <i>J</i> = 8.5 Hz, 1H), 7.47 (s, 1H), 6.84 (s, 1H), 6.57-6.64 (m, 1H), 6.22 (d, <i>J</i> = 16.7 Hz, 1H), 5.74 (d, <i>J</i> = 10.6 Hz, 1H), 4.13 (s, 3H), 3.88 (s, 3H), 2.88 (d, <i>J</i> = 10.5 Hz, 2H), 2.43-2.55 (m, 4H), 2.23 (s, 3H), 1.02 (t, <i>J</i> = 5.6 Hz, 6H).
终产物 155	C2		MS (ESI ⁺) m/z = 597.39 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.80 (s, 1H), 8.63 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.87 (d, <i>J</i> = 8.5 Hz, 1H), 7.78 (d, <i>J</i> = 8.5 Hz, 1H), 7.46 (s, 1H), 6.85 (s, 1H), 6.65-6.72 (m, 1H), 6.23 (d, <i>J</i> = 17.0 Hz, 1H), 5.74 (d, <i>J</i> = 11.3 Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H),

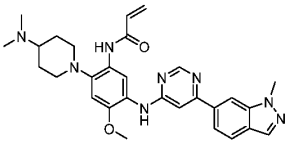
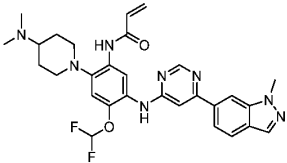
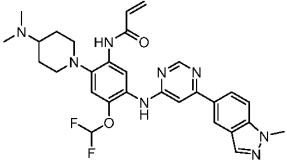
			3.52-3.56 (m, 2H), 3.07 (d, $J = 11.0$ Hz, 2H), 2.81 (d, $J = 10.3$ Hz, 2H), 2.67 (t, $J = 11.1$ Hz, 2H), 2.23-2.26 (m, 1H), 1.79-1.85 (m, 4H), 1.70-1.76 (m, 2H), 1.07 (d, $J = 6.2$ Hz, 6H).
终产物 156	C2		MS (ESI ⁺) $m/z = 610.36$ [M+H] ⁺ . ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.81 (s, 1H), 8.62 (s, 1H), 8.36 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.7$ Hz, 1H), 7.78 (d, $J = 8.7$ Hz, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 6.64-6.70 (m, 1H), 6.25 (d, $J = 15.6$ Hz, 1H), 5.75 (d, $J = 10.2$ Hz, 1H), 4.14 (s, 3H), 3.86 (s, 3H), 3.09 (s, 3H), 2.86 (brs, 2H), 2.62-2.74 (m, 3H), 2.35 (brs, 3H), 2.15 (brs, 3H), 1.84-1.90 (m, 2H), 1.60-1.74 (m, 2H), 1.32 (brs, 3H), 1.04 (d, $J = 6.2$ Hz, 3H).
终产物 157	C2		MS (ESI ⁺) $m/z = 610.31$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.99 (s, 1H), 8.77 (s, 1H), 8.63 (s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.46 (s, 1H), 6.86 (s, 1H), 6.63-6.67 (m, 1H), 6.23 (d, $J = 17.2$ Hz, 1H), 5.73 (d, $J = 10.8$ Hz, 1H), 4.13 (s, 3H), 3.84 (s, 3H), 3.06 (d, $J = 10.8$ Hz, 2H), 2.68 (t, $J = 10.4$ Hz, 2H), 2.52 (brs, 5H), 2.46 (brs, 4H), 2.27-2.30 (m, 1H), 1.85 (d, $J = 10.9$ Hz, 2H), 1.68-1.74 (m, 2H), 0.97 (d, $J = 5.3$ Hz, 6H).

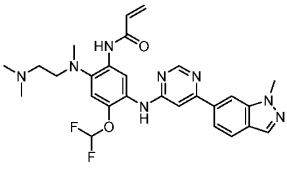
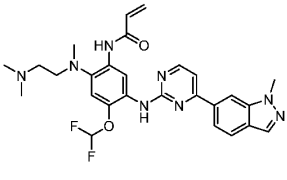
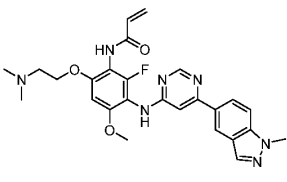
终产物 158	C2		MS (ESI⁺) m/z = 553.30 [M+H]⁺. ¹H NMR (300 MHz, DMSO-<i>d</i>₆) δ 9.12 (s, 1H), 8.84 (s, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.11 (d, J = 0.9 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.49 (s, 1H), 6.87 (s, 1H), 6.58-6.64 (m, 1H), 6.25 (d, J = 17.4 Hz, 1H), 5.75 (d, J = 11.4 Hz, 1H), 4.14 (s, 3H), 3.86 (s, 3H), 3.41 (s, 4H), 3.08-3.13 (m, 3H), 2.71 (t, J = 11.1 Hz, 2H), 2.05 (s, 2H), 1.86 (s, 6H).
终产物 159	C2		MS (ESI⁺) m/z = 543.33 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.03 (s, 1H), 8.80 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 6.89 (s, 1H), 6.58-6.65 (m, 1H), 6.22 (d, J = 17.1 Hz, 1H), 5.73 (d, J = 10.5 Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 3.47 (t, J = 5.8 Hz, 2H), 3.26 (s, 3H), 2.87 (d, J = 6.0 Hz, 4H), 2.64 (s, 4H), 2.56 (t, J = 5.7 Hz, 2H).
终产物 160	C28		MS (ESI⁺) m/z = 563.32 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.18 (s, 1H), 9.12 (s, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.45 (s, 1H), 6.99-7.36 (m, 2H), 6.60-6.67 (m, 1H), 6.25 (d, J = 16.6 Hz, 1H), 5.78 (d, J = 11.0 Hz, 1H), 4.13 (s, 3H), 2.88-2.91 (m, 2H), 2.45-2.47 (m, 4H), 2.23 (s, 3H), 1.02 (d, J = 4.5 Hz, 6H).

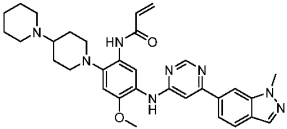
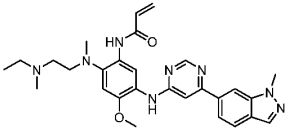
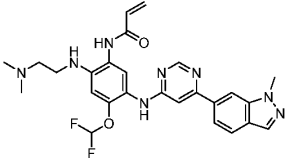
			(m, 1H), 6.27 (d, $J = 17.2$ Hz, 1H), 5.78 (d, $J = 11.6$ Hz, 1H), 4.13 (s, 3H), 3.26-3.14 (m, 1H), 3.08 (s, 3H), 2.79 (s, 2H), 2.65 (t, $J = 10.8$ Hz, 3H), 2.33 (s, 2H), 2.16 (s, 3H), 1.84 (s, 2H), 1.75 (s, 2H), 1.32 (s, 3H), 1.01 (s, 3H).
终产物 164	C28		MS (ESI ⁺) $m/z = 589.29$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.16 (s, 1H), 9.11 (s, 1H), 8.65 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.45 (s, 1H), 6.96-7.33 (m, 2H), 6.64-6.71 (m, 1H), 6.27 (d, $J = 17.0$ Hz, 1H), 5.78 (d, $J = 11.6$ Hz, 1H), 4.13 (s, 3H), 3.06 (d, $J = 10.9$ Hz, 2H), 2.63-2.69 (m, 7H), 1.98 (brs, 2H), 1.75 (brs, 6H).
终产物 165	C28		MS (ESI ⁺) $m/z = 549.29$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- d_6) δ 9.46 (s, 1H), 9.12 (s, 1H), 8.66 (s, 1H), 8.60 (s, 1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.48 (s, 1H), 6.99-7.29 (m, 2H), 6.60-6.64 (m, 1H), 6.26 (dd, $J = 17.0, 1.4$ Hz, 1H), 5.78 (d, $J = 11.7$ Hz, 1H), 4.13 (s, 3H), 3.59-3.60 (m, 1H), 2.57 (s, 4H), 2.40-2.49 (m, 3H), 2.23 (s, 3H), 1.91-1.93 (m, 1H), 1.73-1.75 (m, 1H).
终产物 166	C2		MS (ESI ⁺) $m/z = 555.28$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.06 (s, 1H), 8.83 (s, 1H), 8.64 (s, 1H), 8.45 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H),

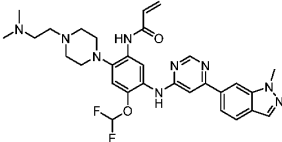
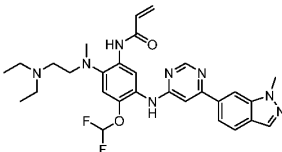
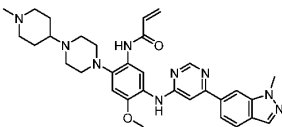
			7.48 (s, 1H), 6.87 (s, 1H), 6.65-6.72 (m, 1H), 6.25 (d, $J = 17.1$ Hz, 1H), 5.76 (d, $J = 10.0$ Hz, 1H), 4.16 (s, 3H), 3.85 (s, 3H), 3.25-3.29 (m, 1H), 3.10-3.20 (m, 4H), 2.81-2.85 (m, 2H), 2.51-2.55 (m, 2H), 1.76-2.04 (m, 4H), 1.23-1.30 (m, 6H).
终产物 167	C28		MS (ESI ⁺) $m/z = 591.25$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 9.09 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.43 (s, 1H), 6.95-7.32 (m, 2H), 6.68-6.75 (m, 1H), 6.27 (d, $J = 18.0$ Hz, 1H), 5.78 (d, $J = 11.2$ Hz, 1H), 4.13 (s, 3H), 3.06 (d, $J = 11.2$ Hz, 2H), 2.52-2.67 (m, 7H), 1.75 (s, 4H), 0.99 (t, $J = 7.2$ Hz, 6H).
终产物 168	C11		MS (ESI ⁺) $m/z = 591.26$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.12 (s, 1H), 9.01 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 8.08 (d, $J = 9.2$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.35 (s, 1H), 6.94-7.31 (m, 2H), 6.68-6.75 (m, 1H), 6.27 (dd, $J = 16.8, 1.2$ Hz, 1H), 5.76 (dd, $J = 6.8, 2.8$ Hz, 1H), 4.09 (s, 3H), 3.06 (d, $J = 11.2$ Hz, 2H), 2.53-2.68 (m, 7H), 1.75 (brs, 4H), 0.99 (t, $J = 7.2$ Hz, 6H).
终产物 169	C2		MS (ESI ⁺) $m/z = 488.25$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.71 (s, 1H), 8.81 (s, 1H), 8.62 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 8.10 (s, 1H), 7.86 (d, $J = 8.5$ Hz, 1H), 7.76 (dd, $J = 8.5, 1.0$ Hz,

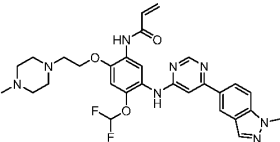
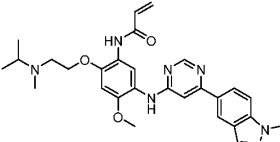
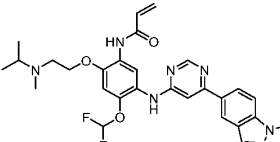
			1H), 7.38 (s, 1H), 6.93 (d, $J = 9.9$ Hz, 1H), 6.45-6.51 (m, 1H), 6.22 (dd, $J = 17.0, 1.7$ Hz, 1H), 5.74 (dd, $J = 10.2, 1.6$ Hz, 1H), 4.19 (t, $J = 5.6$ Hz, 2H), 4.13 (s, 3H), 3.86 (s, 3H), 2.61 (t, $J = 5.2$ Hz, 2H), 2.27 (s, 6H).
终产物 170	C28		MS (ESI ⁺) $m/z = 524.19$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.78 (s, 1H), 9.10 (s, 1H), 8.63 (s, 1H), 8.44 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.89 (d, $J = 8.5$ Hz, 1H), 7.78 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.37 (s, 1H), 7.00-7.30 (m, 2H), 6.51-6.57 (m, 1H), 6.25 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.77 (dd, $J = 10.5, 1.5$ Hz, 1H), 4.19 (t, $J = 5.7$ Hz, 2H), 4.13 (s, 3H), 2.64 (t, $J = 5.2$ Hz, 2H), 2.27 (s, 6H).
终产物 171	C11		MS (ESI ⁺) $m/z = 524.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.76 (s, 1H), 9.02 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.44 (s, 1H), 8.18 (s, 1H), 8.09 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.00-7.30 (m, 3H), 6.51-6.57 (m, 1H), 6.26 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.78 (dd, $J = 10.0, 1.5$ Hz, 1H), 4.19 (t, $J = 5.5$ Hz, 2H), 4.09 (s, 3H), 2.65 (d, $J = 5.0$ Hz, 2H), 2.27 (s, 6H).
终产物 172	C17		MS (ESI ⁺) $m/z = 519.21$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.60 (s, 1H), 8.81 (s, 1H), 8.55 (s, 1H), 8.31 (s, 1H), 8.09 (s, 1H), 7.85 (d, $J = 8.5$ Hz, 1H), 7.76 (d, $J = 8.7$ Hz, 1H), 7.03 (s, 1H), 6.68 (s, 1H), 6.60-6.67 (m, 1H), 6.22

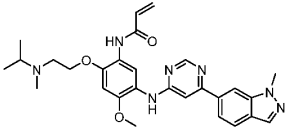
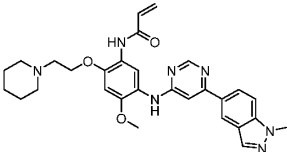
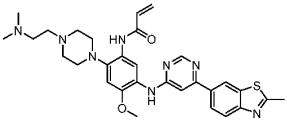
			(d, $J = 16.0$ Hz, 1H), 5.74 (d, $J = 10.4$ Hz, 1H), 4.13 (s, 3H), 3.82 (s, 3H), 3.07-3.17 (m, 4H), 2.78 (s, 3H), 2.27 (brs, 6H).
终产物 173	C2		MS (ESI ⁺) $m/z = 527.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.6$ Hz, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 6.64-6.71 (m, 1H), 6.24 (dd, $J = 17.0, 1.6$ Hz, 1H), 5.75 (d, $J = 10.9$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.07-3.12 (m, 2H), 2.70 (t, $J = 11.0$ Hz, 2H), 2.40-2.49 (m, 7H), 1.90-1.93 (m, 2H), 1.75-1.77 (m, 2H).
终产物 174	C28		MS (ESI ⁺) $m/z = 563.27$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.17 (s, 1H), 9.12 (s, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.79 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.44 (s, 1H), 7.00-7.29 (m, 2H), 6.68-6.74 (m, 1H), 6.27 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.78 (dd, $J = 11.5, 1.0$ Hz, 1H), 4.13 (s, 3H), 3.08 (d, $J = 11.4$ Hz, 2H), 2.63 (t, $J = 11.4$ Hz, 2H), 2.27 (brs, 7H), 1.86 (d, $J = 11.0$ Hz, 2H), 1.69-1.75 (m, 2H).
终产物 175	C11		MS (ESI ⁺) $m/z = 563.25$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 9.03 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.09 (dd, $J = 8.9, 1.2$ Hz, 1H), 7.76 (d, $J = 8.9$ Hz, 1H), 7.35 (s, 1H), 7.00-7.29 (m, 2H),

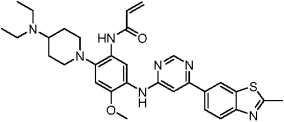
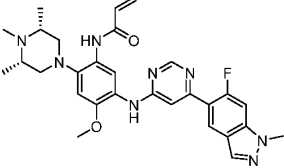
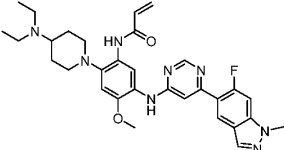
			6.68-6.73 (m, 1H), 6.27 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.78 (d, $J = 11.6$ Hz, 1H), 4.09 (s, 3H), 3.07 (d, $J = 8.4$ Hz, 2H), 2.63 (t, $J = 10.9$ Hz, 2H), 2.27-2.14 (m, 7H), 1.84 (d, $J = 11.2$ Hz, 2H), 1.69-1.74 (m, 2H).
终产物 176	C28		MS (ESI ⁺) $m/z = 536.81$ [M+H] ⁺ .
终产物 177	C15		MS (ESI ⁺) $m/z = 537.23$ [M+H] ⁺ . ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 10.28 (s, 1H), 9.06 (s, 1H), 8.64 (s, 1H), 8.56 (s, 1H), 8.54 (s, 1H), 8.51 (s, 1H), 8.12 (d, $J = 0.9$ Hz, 1H), 7.99 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 7.58 (d, $J = 5.4$ Hz, 1H), 6.88-7.37 (m, 1H), 6.59-6.37 (m, 1H), 6.31 (d, $J = 1.8$ Hz, 1H), 5.83 (dd, $J = 10.2, 2.1$ Hz, 1H), 4.12 (d, $J = 10.8$ Hz, 3H), 2.88 (s, 2H), 2.72 (s, 3H), 2.37 (s, 2H), 2.25 (s, 6H).
终产物 178	C16		MS (ESI ⁺) $m/z = 506.24$ [M+H] ⁺ . ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 9.43 (s, 1H), 8.77 (s, 1H), 8.52 (s, 1H), 8.48 (s, 1H), 8.18 (s, 1H), 8.08 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 6.97 (brs, 1H), 6.74 (s, 1H), 6.42-6.51 (m, 1H), 6.22 (dd, $J = 16.8, 1.8$ Hz, 1H), 5.73 (d, $J = 10.2, 1.8$ Hz, 1H), 4.19 (t, $J = 5.7$ Hz, 2H), 4.09 (s, 3H), 3.86 (s, 3H), 2.65 (t, $J = 5.7$ Hz, 2H), 2.24 (s, 6H).

终产物 179	C2		MS (ESI ⁺) m/z = 567.28 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.87 (d, <i>J</i> = 8.5 Hz, 1H), 7.78 (d, <i>J</i> = 8.8 Hz, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 6.64-6.71 (m, 1H), 6.24 (d, <i>J</i> = 16.9 Hz, 1H), 5.75 (d, <i>J</i> = 10.5 Hz, 1H), 4.14 (s, 3H), 3.85 (s, 3H), 3.34-3.35 (m, 1H), 3.10 (brs, 3H), 2.69 (s, 2H), 2.51 (brs, 2H), 2.33-2.49 (m, 1H), 1.42-1.94 (m, 10H).
终产物 180	C2		MS (ESI ⁺) m/z = 515.25 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.92 (s, 1H), 8.83 (s, 1H), 8.65 (s, 2H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, <i>J</i> = 8.5 Hz, 1H), 7.78 (dd, <i>J</i> = 8.5, 1.0 Hz, 1H), 7.48 (s, 1H), 7.01 (s, 1H), 6.53 (brs, 1H), 6.25 (d, <i>J</i> = 16.7 Hz, 1H), 5.77 (d, <i>J</i> = 10.5 Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 2.89 (brs, 2H), 2.72 (brs, 3H), 2.41-2.45 (m, 4H), 2.20 (s, 3H), 1.01 (s, 3H).
终产物 181	C28		MS (ESI ⁺) m/z = 522.77 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.53 (s, 1H), 8.91 (s, 1H), 8.58 (s, 1H), 8.32 (s, 1H), 8.10 (s, 1H), 7.85 (d, <i>J</i> = 8.4 Hz, 1H), 7.76 (d, <i>J</i> = 8.5 Hz, 1H), 7.53 (s, 1H), 6.95-7.32 (m, 2H), 6.55 (s, 1H), 6.46-6.53 (m, 1H), 6.23 (dd, <i>J</i> = 17.1, 1.8 Hz, 1H), 5.75 (dd, <i>J</i> = 10.2, 2.0 Hz, 1H), 5.14-5.17 (m, 1H), 4.13 (s, 3H), 3.16 (q, <i>J</i> = 7.0 Hz, 2H), 2.47-2.49 (m, 2H), 2.20 (s, 6H).

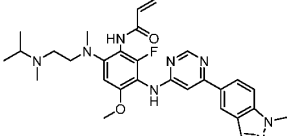
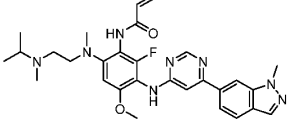
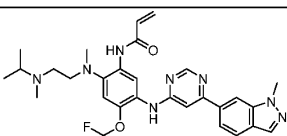
终产物 182	C28		MS (ESI ⁺) m/z = 592.27 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 9.09 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.87 (d, <i>J</i> = 8.4 Hz, 1H), 7.79 (d, <i>J</i> = 8.4, 0.8 Hz, 1H), 7.45 (s, 1H), 6.96-7.33 (m, 2H), 6.61-6.68 (m, 1H), 6.25 (dd, <i>J</i> = 17.2, 1.6 Hz, 1H), 5.77 (d, <i>J</i> = 12.0, 1.6 Hz, 1H), 4.13 (s, 3H), 2.84 (d, <i>J</i> = 4.4 Hz, 4H), 2.63 (s, 4H), 2.45-2.50 (m, 2H), 2.32-2.39 (m, 2H), 2.16 (s, 6H).
终产物 183	C28		MS (ESI ⁺) m/z = 565.51 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 9.11 (s, 1H), 8.65 (s, 1H), 8.62 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.87 (d, <i>J</i> = 8.5 Hz, 1H), 7.78 (dd, <i>J</i> = 8.8, 1.2 Hz, 1H), 7.42 (s, 1H), 6.94-7.31 (m, 2H), 6.46-6.53 (m, 1H), 6.28 (dd, <i>J</i> = 17.0, 1.6 Hz, 1H), 5.80 (dd, <i>J</i> = 10.4, 1.6 Hz, 1H), 4.13 (s, 3H), 2.85 (t, <i>J</i> = 5.8 Hz, 2H), 2.71 (s, 3H), 2.51-2.55 (m, 6H), 0.96 (t, <i>J</i> = 7.1 Hz, 6H).
终产物 184	C2		MS (ESI ⁺) m/z = 582.32 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.83 (d, <i>J</i> = 8.9 Hz, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.87 (d, <i>J</i> = 8.5 Hz, 1H), 7.79 (d, <i>J</i> = 8.5 Hz, 1H), 7.48 (s, 1H), 6.90 (s, 1H), 6.60-6.66 (m, 1H), 6.23 (dd, <i>J</i> = 17.0, 1.0 Hz, 1H), 5.74 (d, <i>J</i> = 10.8 Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 2.83-2.88 (m, 6H), 2.70 (brs, 4H), 2.18-2.24 (m, 4H),

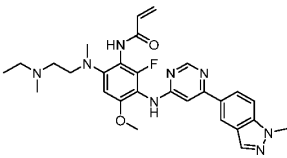
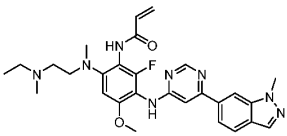
			1.91-1.93 (m, 2H), 1.78 (d, $J = 11.4$ Hz, 2H), 1.46-1.50 (m, 2H).
终产物 185	C11		MS (ESI ⁺) $m/z = 579.00$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- d_6) δ 9.35 (s, 1H), 9.01 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.34 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.75 (d, $J = 8.5$ Hz, 1H), 7.01-7.31 (m, 3H), 6.62-6.67 (m, 1H), 6.25 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.77 (dd, $J = 10.0, 1.5$ Hz, 1H), 4.20 (t, $J = 6.0$ Hz, 2H), 4.09 (s, 3H), 2.74 (t, $J = 5.5$ Hz, 2H), 2.51 (brs, 4H), 2.31 (s, 4H), 2.14 (s, 3H).
终产物 186	C1		MS (ESI ⁺) $m/z = 515.84$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- d_6) δ 9.35 (s, 1H), 8.74 (s, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 8.17 (s, 1H), 8.06 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.25 (s, 1H), 6.92 (s, 1H), 6.50-6.56 (m, 1H), 6.23 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.73 (dd, $J = 10.0, 1.5$ Hz, 1H), 4.15 (t, $J = 6.0$ Hz, 2H), 4.09 (s, 3H), 3.85 (s, 3H), 2.87-2.90 (m, 1H), 2.74 (t, $J = 6.0$ Hz, 2H), 2.26 (s, 3H), 0.99 (d, $J = 6.5$ Hz, 6H).
终产物 187	C11		MS (ESI ⁺) $m/z = 551.97$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.43 (s, 1H), 8.99 (s, 1H), 8.58 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 8.8, 1.6$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 6.96-7.33 (m, 3H), 6.54-6.59 (m, 1H), 6.25 (dd, $J = 17.0, 1.8$ Hz, 1H), 5.76

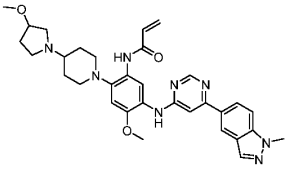
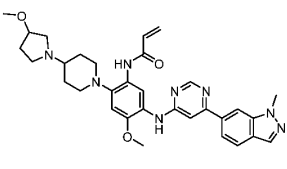
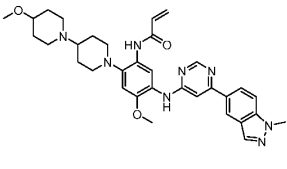
			(dd, $J = 10.0, 1.6$ Hz, 1H), 4.13 (t, $J = 5.6$ Hz, 2H), 4.08 (s, 3H), 2.95-2.78 (m, 1H), 2.74 (t, $J = 5.9$ Hz, 2H), 2.24 (s, 3H), 0.97 (d, $J = 6.5$ Hz, 6H).
终产物 188	C2		MS (ESI ⁺) $m/z = 515.98$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.35 (s, 1H), 8.79 (s, 1H), 8.62 (s, 1H), 8.32 (s, 2H), 8.10 (s, 1H), 7.86 (d, $J = 8.5$ Hz, 1H), 7.76 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.35 (s, 1H), 6.92 (s, 1H), 6.50-6.57 (m, 1H), 6.22 (dd, $J = 17.0, 1.7$ Hz, 1H), 5.72 (dd, $J = 11.7, 1.6$ Hz, 1H), 4.12-4.16 (m, 5H), 3.85 (s, 3H), 2.85-2.88 (m, 1H), 2.72 (t, $J = 5.8$ Hz, 2H), 2.25 (s, 3H), 0.98 (d, $J = 6.5$ Hz, 6H).
终产物 189	C1		MS (ESI ⁺) $m/z = 527.76$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (s, 1H), 8.73 (s, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 8.26 (s, 1H), 8.17 (s, 1H), 8.06 (dd, $J = 8.9, 1.4$ Hz, 1H), 7.74 (d, $J = 8.9$ Hz, 1H), 7.25 (s, 1H), 6.91 (s, 1H), 6.56-6.61 (m, 1H), 6.22 (dd, $J = 17.0, 1.7$ Hz, 1H), 5.73 (dd, $J = 10.3, 1.4$ Hz, 1H), 4.21 (t, $J = 6.0$ Hz, 2H), 4.09 (s, 3H), 3.86 (s, 3H), 2.69 (t, $J = 5.8$ Hz, 2H), 2.46-2.50 (m, 4H), 1.48-1.53 (m, 4H), 1.38-1.40 (m, 2H).
终产物 190	C9		MS (ESI ⁺) $m/z = 572.99$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.81 (s, 1H), 8.75 (d, $J = 1.2$ Hz, 1H), 8.61 (s, 1H), 8.31 (s, 1H), 8.11 (dd, $J = 8.6, 1.6$ Hz, 1H), 8.01 (d, $J = 8.6$ Hz,

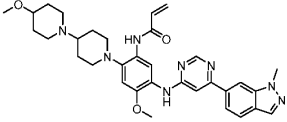
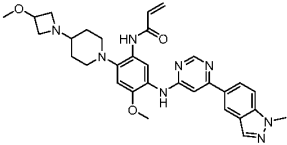
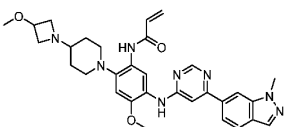
			1H), 7.40 (s, 1H), 6.89 (s, 1H), 6.59-6.65 (m, 1H), 6.25 (d, $J = 17.1$ Hz, 1H), 5.74 (d, $J = 10.8$ Hz, 1H), 3.85 (s, 3H), 2.86 (d, $J = 4.4$ Hz, 4H), 2.83 (s, 3H), 2.62 (s, 4H), 2.46 (d, $J = 10.4$ Hz, 2H), 2.39 (d, $J = 7.1$ Hz, 2H), 2.16 (s, 6H).
终产物 191	C9		MS (ESI ⁺) $m/z = 571.64$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.81 (s, 1H), 8.75 (d, $J = 1.1$ Hz, 1H), 8.61 (s, 1H), 8.33 (s, 1H), 8.11 (dd, $J = 8.6, 1.5$ Hz, 1H), 8.01 (d, $J = 8.5$ Hz, 1H), 7.38 (s, 1H), 6.85 (d, $J = 13.3$ Hz, 1H), 6.60-6.69 (m, 1H), 6.26 (d, $J = 17.8$ Hz, 1H), 5.75 (d, $J = 10.9$ Hz, 1H), 3.83 (s, 3H), 3.06 (d, $J = 10.6$ Hz, 2H), 2.83 (s, 3H), 2.65-2.69 (m, 2H), 2.53-2.66 (m, 5H), 1.73-1.74 (m, 4H), 0.99 (t, $J = 7.0$ Hz, 6H).
终产物 192	C12		MS (ESI ⁺) $m/z = 544.86$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.96 (s, 1H), 8.59 (s, 1H), 8.46 (d, $J = 7.5$ Hz, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 7.68 (d, $J = 12.0$ Hz, 1H), 7.19 (s, 1H), 6.83 (s, 1H), 6.55-6.61 (m, 1H), 6.20 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.72 (d, $J = 8.8$ Hz, 1H), 4.05 (s, 3H), 3.83 (s, 3H), 2.87 (d, $J = 10.5$ Hz, 2H), 2.54 (s, 2H), 2.43 (s, 2H), 2.23 (s, 3H), 1.02 (d, $J = 6.0$ Hz, 6H).
终产物 193	C12		MS (ESI ⁺) $m/z = 573.31$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.94 (s, 1H), 8.58 (s, 1H), 8.47 (d, $J = 7.4$ Hz, 1H), 8.29 (s, 1H), 8.19 (d, $J =$

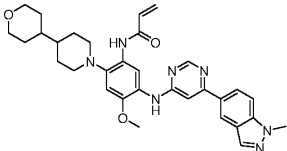
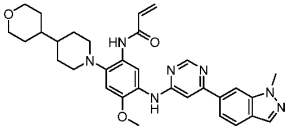
			0.8 Hz, 1H), 7.67 (d, $J = 12.3$ Hz, 1H), 7.18 (s, 1H), 6.85 (s, 1H), 6.63-6.70 (m, 1H), 6.22 (dd, $J = 17.0, 1.7$ Hz, 1H), 5.73 (d, $J = 11.2$ Hz, 1H), 4.04 (s, 3H), 3.81 (s, 3H), 3.05 (d, $J = 10.8$ Hz, 2H), 2.65-2.72 (m, 2H), 2.53-2.60 (m, 5H), 1.74 (brs, 4H), 0.99 (t, $J = 7.1$ Hz, 6H).
终产物 194	C12		MS (ESI ⁺) $m/z = 506.77$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.65 (s, 1H), 8.93 (s, 1H), 8.58 (s, 1H), 8.46 (d, $J = 7.4$ Hz, 1H), 8.30 (s, 1H), 8.19 (s, 1H), 7.67 (d, $J = 12.3$ Hz, 1H), 7.12 (brs, 1H), 6.93 (s, 1H), 6.44-6.50 (m, 1H), 6.21 (dd, $J = 17.0, 1.8$ Hz, 1H), 5.73 (dd, $J = 10.2, 1.6$ Hz, 1H), 4.19 (t, $J = 5.6$ Hz, 2H), 4.04 (s, 3H), 3.82 (s, 3H), 2.60 (t, $J = 5.6$ Hz, 2H), 2.26 (s, 6H).
终产物 195	C12		MS (ESI ⁺) $m/z = 531.30$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.29 (s, 1H), 8.96 (s, 1H), 8.60 (s, 1H), 8.46-8.51 (m, 2H), 8.19 (s, 1H), 7.68 (d, $J = 12.0$ Hz, 1H), 7.23 (s, 1H), 6.97 (s, 1H), 6.54-6.61 (m, 1H), 6.22 (dd, $J = 17.2, 1.6$ Hz, 1H), 5.73 (dd, $J = 11.6, 1.6$ Hz, 1H), 4.05 (s, 3H), 3.81 (s, 3H), 3.62 (brs, 1H), 2.58 (s, 3H), 2.53-2.55 (m, 1H), 2.47-2.49 (m, 1H), 2.39-2.43 (m, 2H), 2.22 (s, 3H), 1.90-1.92 (m, 1H), 1.72-1.74 (m, 1H).
终产物 196	C2		MS (ESI ⁺) $m/z = 529.27$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.81 (s, 1H), 8.81 (s, 1H), 8.67 (s, 1H), 8.64 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.86 (d, $J = 12.3$ Hz, 1H), 7.12 (brs, 1H), 6.93 (s, 1H), 6.44-6.50 (m, 1H), 6.21 (dd, $J = 17.0, 1.8$ Hz, 1H), 5.73 (dd, $J = 10.2, 1.6$ Hz, 1H), 4.19 (t, $J = 5.6$ Hz, 2H), 4.04 (s, 3H), 3.82 (s, 3H), 2.60 (t, $J = 5.6$ Hz, 2H), 2.26 (s, 6H).

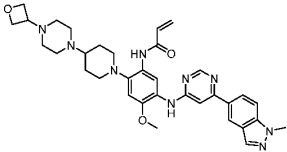
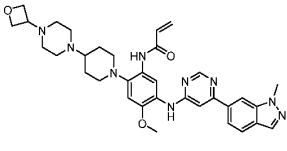
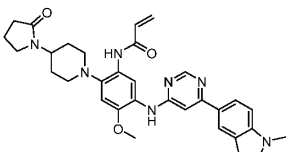
			= 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 6.99 (s, 1H), 6.35-6.46 (m, 1H), 6.24 (d, J = 16.8 Hz, 1H), 5.76 (d, J = 10.0 Hz, 1H), 4.13 (s, 3H), 3.84 (s, 3H), 2.82 (brs, 3H), 2.73 (s, 3H), 2.44-2.50 (m, 2H), 2.19 (s, 3H), 0.97 (d, J = 6.1 Hz, 6H).
终产物 197	C16		MS (ESI ⁺) m/z = 547.26 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- d_6) δ 9.42 (s, 1H), 8.72 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 8.15 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 6.94 (brs, 1H), 6.56 (s, 1H), 6.46-6.52 (m, 1H), 6.22 (d, J = 17.0 Hz, 1H), 5.72 (d, J = 10.0 Hz, 1H), 4.08 (s, 3H), 3.81 (s, 3H), 3.01 (s, 2H), 2.81 (s, 3H), 2.71-2.76 (m, 1H), 2.51 (brs, 2H), 2.09 (s, 3H), 0.91 (d, J = 6.5 Hz, 6H).
终产物 198	C17		MS (ESI ⁺) m/z = 547.24 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- d_6) δ 9.46 (s, 1H), 8.79 (s, 1H), 8.54 (s, 1H), 8.30 (s, 1H), 8.10 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 6.99 (brs, 1H), 6.57 (s, 1H), 6.47-6.53 (m, 1H), 6.22 (d, J = 17.0 Hz, 1H), 5.72 (d, J = 10.5 Hz, 1H), 4.13 (s, 3H), 3.81 (s, 3H), 3.01 (t, J = 6.5 Hz, 2H), 2.81 (s, 3H), 2.70-2.74 (m, 1H), 2.52 (s, 2H), 2.08 (s, 3H), 0.91 (d, J = 6.5 Hz, 6H).
终产物 199	C28		MS (ESI ⁺) m/z = 565.28 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- d_6) δ 9.98 (s, 1H), 9.19 (s, 1H), 8.67 (s, 1H), 8.64 (s,

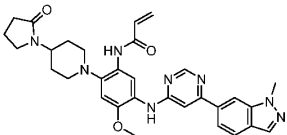
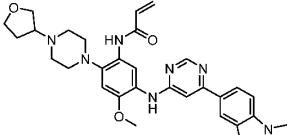
			1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.43 (s, 1H), 6.97-7.27 (m, 2H), 6.41-6.46 (m, 1H), 6.28 (d, $J = 16.5$ Hz, 1H), 5.80 (d, $J = 11.0$ Hz, 1H), 4.13 (s, 3H) 2.71-2.88 (m, 6H), 2.46 (s, 2H), 2.23 (s, 3H). 0.98 (d, $J = 6.0$ Hz, 6H).
终产物 200	C16		MS (ESI ⁺) $m/z = 533.32$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.46 (s, 1H), 8.72 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 8.15 (s, 1H), 8.05 (d, $J = 8.9$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 6.93 (brs, 1H), 6.57 (s, 1H), 6.46-6.52 (m, 1H), 6.22 (d, $J = 17.1$ Hz, 1H), 5.73 (d, $J = 10.7$ Hz, 1H), 4.08 (s, 3H), 3.81 (s, 3H), 3.03 (t, $J = 6.9$ Hz, 2H), 2.80 (s, 3H), 2.47-2.50 (m, 2H), 2.34 (q, $J = 7.0$ Hz, 2H), 2.12 (s, 3H), 0.95 (t, $J = 7.1$ Hz, 3H).
终产物 201	C17		MS (ESI ⁺) $m/z = 533.32$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.50 (s, 1H), 8.80 (s, 1H), 8.55 (s, 1H), 8.31 (s, 1H), 8.10 (s, 1H), 7.85 (d, $J = 8.5$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.01 (s, 1H), 6.58 (s, 1H), 6.46-6.52 (m, 1H), 6.21 (d, $J = 17.0$ Hz, 1H), 5.73 (d, $J = 11.0$ Hz, 1H), 4.14 (s, 3H), 3.81 (s, 3H), 3.04 (t, $J = 7.0$ Hz, 2H), 2.81 (s, 3H), 2.48 (s, 2H), 2.34 (q, $J = 7.0$ Hz, 2H), 2.09 (s, 3H), 1.04 (d, $J = 7.0$ Hz, 3H).

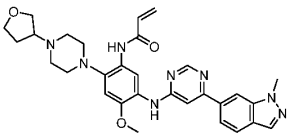
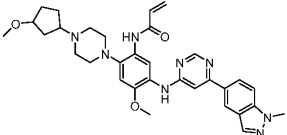
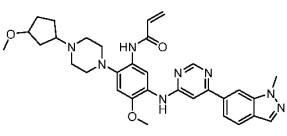
终产物 202	C1		MS (ESI ⁺) m/z = 583.33 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.20 (d, J = 26.7 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.36 (s, 1H), 6.86 (s, 1H), 6.60-6.66 (m, 1H), 6.24 (d, J = 17.0 Hz, 1H), 5.74 (d, J = 10.5 Hz, 1H), 4.08 (s, 3H), 3.81-3.87 (m, 1H), 3.84 (s, 3H), 3.18 (s, 3H), 3.02 (d, J = 11.5 Hz, 2H), 2.62-2.75 (m, 4H), 2.52-2.53 (m, 1H), 2.46-2.48 (m, 1H), 2.09-2.15 (m, 1H), 1.90-2.00 (m, 3H), 1.65-1.69 (m, 3H).
终产物 203	C2		MS (ESI ⁺) m/z = 583.33 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 6.86 (s, 1H), 6.60-6.66 (m, 1H), 6.23 (d, J = 17.0 Hz, 1H), 5.74 (d, J = 10.5 Hz, 1H), 4.13 (s, 3H), 3.85 (s, 4H), 3.18 (s, 3H), 3.02 (d, J = 11.0 Hz, 2H), 2.63-2.75 (m, 4H), 2.52-2.54 (m, 1H), 2.46-2.48 (m, 1H), 2.09-2.20 (m, 1H), 1.90-1.96 (m, 3H), 1.65-1.69 (m, 3H).
终产物 204	C1		MS (ESI ⁺) m/z = 597.36 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.73 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.36 (s, 1H), 6.84 (s, 1H), 6.60-6.68 (m, 1H), 6.24 (d, J = 17.0 Hz, 1H), 5.74 (d, J

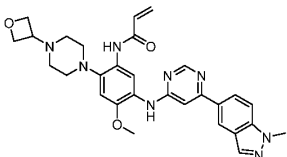
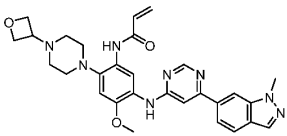
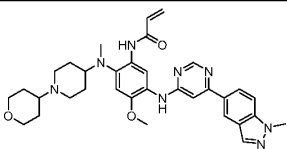
			= 10.5 Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.23 (s, 3H), 3.15-3.20 (m, 1H), 3.06 (d, J = 10.5 Hz, 2H), 2.79-2.81 (m, 2H), 2.67 (t, J = 11.0 Hz, 2H), 2.28-2.34 (m, 1H), 2.26 (t, J = 9.5 Hz, 2H), 1.79-1.86 (m, 6H), 1.38-1.40 (m, 2H).
终产物 205	C2		MS (ESI ⁺) m/z = 597.29 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 6.85 (s, 1H), 6.65-6.70 (m, 1H), 6.24 (d, J = 17.0 Hz, 1H), 5.74 (d, J = 10.0 Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.07-3.23 (m, 6H), 2.80 (s, 2H), 2.66 (s, 2H), 2.26-2.36 (m, 3H), 1.78-1.97 (m, 6H), 1.40 (s, 2H).
终产物 206	C1		MS (ESI ⁺) m/z = 569.26 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.36 (s, 1H), 6.85 (s, 1H), 6.60-6.67 (m, 1H), 6.23 (d, J = 16.8 Hz, 1H), 5.73 (d, J = 9.2 Hz, 1H), 4.08 (s, 3H), 3.95 (s, 1H), 3.84 (s, 3H), 3.66 (t, J = 5.2 Hz, 2H), 3.50 (s, 2H), 3.16 (s, 3H), 2.80 (s, 2H), 2.65 (t, J = 13.0 Hz, 2H), 2.13 (s, 1H), 1.75 (s, 2H), 1.47 (s, 2H).
终产物 207	C2		MS (ESI ⁺) m/z = 569.32 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.80 (s, 1H), 8.63 (s, 1H), 8.37 (s,

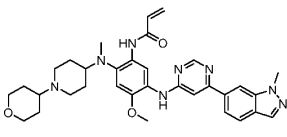
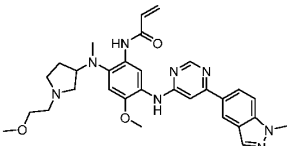
			1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.46 (s, 1H), 6.85 (s, 1H), 6.61-6.68 (m, 1H), 6.23 (d, $J = 16.8$ Hz, 1H), 5.73 (d, $J = 10.0$ Hz, 1H), 4.13 (s, 3H), 3.95 (s, 1H), 3.85 (s, 3H), 3.50 (s, 3H), 3.16 (s, 2H), 2.98 (s, 2H), 2.76 (s, 2H), 2.65 (t, $J = 10.0$ Hz, 2H), 2.13 (s, 1H), 1.75 (s, 2H), 1.47 (s, 2H).
终产物 208	C1		MS (ESI ⁺) $m/z = 568.37$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.07 (d, $J = 8.9$ Hz, 1H), 7.74 (d, $J = 8.9$ Hz, 1H), 7.37 (s, 1H), 6.85 (s, 1H), 6.64-6.68 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.73 (d, $J = 11.0$ Hz, 1H), 4.08 (s, 3H), 3.84-3.89 (m, 5H), 3.28 (t, $J = 11.0$ Hz, 2H), 3.05 (d, $J = 5.0$ Hz, 2H), 2.63 (d, $J = 11.0$ Hz, 2H), 1.76 (d, $J = 11.0$ Hz, 2H), 1.63 (d, $J = 12.0$ Hz, 2H), 1.45 (q, $J = 11.0$ Hz, 2H), 1.34 (s, 1H), 1.17-1.23 (m, 3H).
终产物 209	C2		MS (ESI ⁺) $m/z = 568.39$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.80 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.86 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.46 (s, 1H), 6.85 (s, 1H), 6.60-6.64 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.73 (d, $J = 10.5$ Hz, 1H), 4.13 (s, 3H), 3.85-3.90 (m, 5H), 3.28 (t, $J = 11.0$ Hz, 2H), 3.05 (d, $J = 10.5$ Hz, 2H), 2.63 (t, $J = 11.0$ Hz,

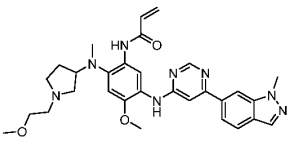
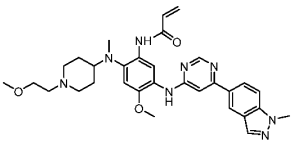
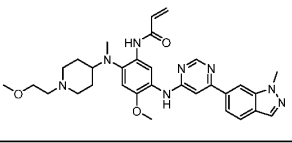
			2H), 1.76 (d, $J = 12.0$ Hz, 2H), 1.63 (d, $J = 12.5$ Hz, 2H), 1.46 (q, $J = 10.0$ Hz, 2H), 1.35 (brs, 1H), 1.18-1.24 (m, 3H).
终产物 210	C1		MS (ESI ⁺) $m/z = 624.37$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.07 (d, $J = 8.7$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.37 (s, 1H), 6.85 (s, 1H), 6.74-6.51 (m, 1H), 6.24 (d, $J = 16.9$ Hz, 1H), 5.74 (d, $J = 10.1$ Hz, 1H), 4.53 (s, 2H), 4.42 (s, 2H), 4.08 (s, 3H), 3.84 (s, 3H), 3.37 (brs, 1H), 3.07 (d, $J = 9.6$ Hz, 2H), 2.67 (t, $J = 11.1$ Hz, 3H), 2.56 (brs, 3H), 2.27 (brs, 5H), 1.83-1.86 (m, 2H), 1.69-1.72 (m, 2H).
终产物 211	C2		MS (ESI ⁺) $m/z = 624.33$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.81 (s, 1H), 8.63 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.78 (d, $J = 8.3$ Hz, 1H), 7.46 (s, 1H), 6.85 (s, 1H), 6.57-6.77 (m, 1H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.0$ Hz, 1H), 4.53 (brs, 2H), 4.42 (brs, 2H), 4.13 (s, 3H), 3.85 (s, 3H), 3.37 (brs, 1H), 3.07 (d, $J = 10.1$ Hz, 2H), 2.68 (t, $J = 11.0$ Hz, 2H), 2.56 (brs, 4H), 2.27 (brs, 5H), 1.83-1.86 (m, 2H), 1.70-1.73 (m, 2H).
终产物 212	C1		MS (ESI ⁺) $m/z = 567.35$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 8.08 (d, J

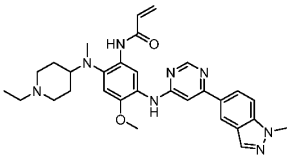
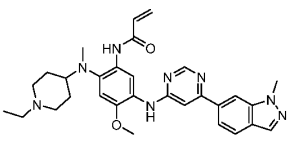
			= 9.0 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.38 (s, 1H), 6.90 (s, 1H), 6.66-6.69 (m, 1H), 6.25 (d, J = 17.6 Hz, 1H), 5.75 (d, J = 10.5 Hz, 1H), 4.06 (s, 3H), 3.86-3.91 (m, 1H), 3.85 (s, 3H), 3.39 (t, J = 6.8 Hz, 2H), 3.08 (d, J = 10.9 Hz, 2H), 2.80 (t, J = 11.4 Hz, 2H), 2.25 (t, J = 8.0 Hz, 2H), 1.92-1.98 (m, 4H), 1.62 (d, J = 10.0 Hz, 2H).
终产物 213	C2		MS (ESI⁺) m/z = 567.36 [M+H]⁺. ¹H NMR (400MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.48 (s, 1H), 6.91 (s, 1H), 6.67-6.73 (m, 1H), 6.23 (d, J = 17.2 Hz, 1H), 5.74 (d, J = 10.8 Hz, 1H), 4.13 (s, 3H), 3.85-3.91 (m, 4H), 3.39 (s, 2H), 3.07 (d, J = 10.4 Hz, 2H), 2.80 (t, J = 10.4 Hz, 2H), 2.24 (t, J = 7.6 Hz, 2H), 1.95 (s, 4H), 1.62 (d, J = 10.4 Hz, 2H).
终产物 214	C1		MS (ESI⁺) m/z = 555.35 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.76 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.39 (s, 1H), 6.88 (s, 1H), 6.60-6.67 (m, 1H), 6.23 (d, J = 16.8 Hz, 1H), 5.74 (d, J = 10.0 Hz, 1H), 4.08 (s, 3H), 3.80-3.85 (m, 5H), 3.52-3.70 (m, 2H), 2.97 (s, 1H), 2.88 (s, 4H), 2.65 (s, 2H), 2.56 (s, 2H), 2.00-2.01 (m, 1H), 1.78-1.80 (m, 1H).

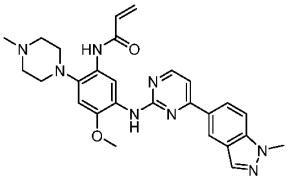
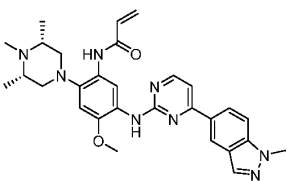
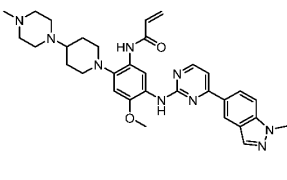
终产物 215	C2		MS (ESI ⁺) m/z = 555.35 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 6.88 (s, 1H), 6.60-6.67 (m, 1H), 6.23 (d, J = 16.8 Hz, 1H), 5.74 (d, J = 10.4 Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.81 (d, J = 6.4 Hz, 2H), 3.67 (q, J = 7.6 Hz, 1H), 3.51 (d, J = 6.8 Hz, 1H), 2.97 (s, 1H), 2.88 (s, 4H), 2.65 (s, 2H), 2.57 (s, 2H), 2.01-2.02 (m, 1H), 1.77-1.79 (m, 1H).
终产物 216	C1		MS (ESI ⁺) m/z = 583.38 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.08 (dd, J = 9.2, 1.6 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.39 (s, 1H), 6.89 (s, 1H), 6.62-6.68 (m, 1H), 6.23 (d, J = 16.9 Hz, 1H), 5.73 (d, J = 10.7 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 3.71-3.75 (m, 1H), 3.17 (s, 3H), 2.88 (s, 4H), 2.54-2.60 (m, 5H), 2.16-2.18 (m, 1H), 1.74-1.78 (m, 1H), 1.65-1.68 (m, 2H), 1.42-1.49 (m, 1H), 1.28-1.30 (m, 1H).
终产物 217	C2		MS (ESI ⁺) m/z = 583.38 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.06 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.48 (s, 1H), 6.90 (s, 1H), 6.59-6.64 (m,

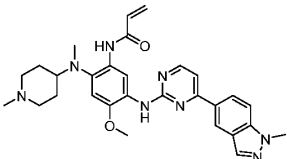
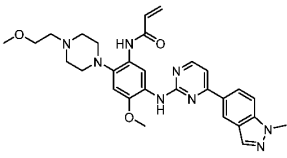
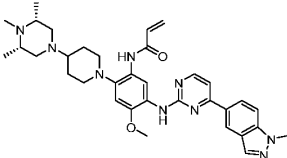
			1H), 6.23 (d, $J = 16.9$ Hz, 1H), 5.73 (d, $J = 10.8$ Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 3.81-3.65 (m, 1H), 3.17 (s, 3H), 2.88 (s, 4H), 2.75-2.52 (m, 5H), 2.25-2.12 (m, 1H), 1.75-1.77 (m, 1H), 1.64-1.68 (m, 2H), 1.48-1.51 (m, 1H), 1.30-1.36 (m, 1H).
终产物 218	C1		MS (ESI ⁺) $m/z = 541.26$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.39 (s, 1H), 6.91 (s, 1H), 6.58-6.65 (m, 1H), 6.23 (d, $J = 16.8$ Hz, 1H), 5.73 (d, $J = 10.2$ Hz, 1H), 4.57 (d, $J = 6.1$ Hz, 2H), 4.48 (s, 2H), 4.08 (s, 3H), 3.86 (s, 3H), 3.51 (brs, 1H), 2.91 (brs, 4H), 2.49-2.41 (m, 4H).
终产物 219	C2		MS (ESI ⁺) $m/z = 541.26$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.06 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.48 (s, 1H), 6.91 (s, 1H), 6.59-6.65 (m, 1H), 6.22 (d, $J = 17.2$ Hz, 1H), 5.73 (d, $J = 10.6$ Hz, 1H), 4.58 (t, $J = 6.5$ Hz, 2H), 4.47 (t, $J = 6.1$ Hz, 2H), 4.13 (s, 3H), 3.87 (s, 3H), 3.57-3.43 (m, 1H), 2.91 (t, $J = 4.2$ Hz, 4H), 2.49-2.50 (m, 4H).
终产物 220	C1		MS (ESI ⁺) $m/z = 597.42$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 8.75 (s, 1H), 8.61 (s, 1H), 8.52 (s,

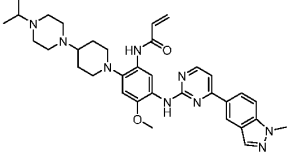
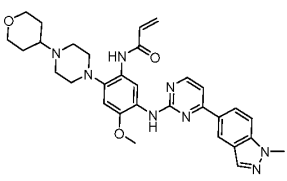
			1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.42 (s, 1H), 6.94 (s, 1H), 6.61-6.67 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.73 (d, $J = 10.5$ Hz, 1H), 4.09 (s, 3H), 3.85 (s, 5H), 3.24 (t, $J = 11.5$ Hz, 2H), 2.88 (d, $J = 10.5$ Hz, 2H), 2.65-2.69 (m, 1H), 2.64 (s, 3H), 2.35 (t, $J = 11.0$ Hz, 1H), 1.99 (t, $J = 11.0$ Hz, 2H), 1.72 (d, $J = 10.4$ Hz, 2H), 1.62 (d, $J = 12.0$ Hz, 2H), 1.52 (q, $J = 10.5$ Hz, 2H), 1.37 (q, $J = 8.5$ Hz, 2H).
终产物 221	C2		MS (ESI ⁺) $m/z = 597.39$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.82 (s, 1H), 8.65 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.51 (s, 1H), 6.94 (s, 1H), 6.61-6.65 (m, 1H), 6.23 (d, $J = 17.5$ Hz, 1H), 5.73 (d, $J = 11.0$ Hz, 1H), 4.14 (s, 3H), 3.89 (s, 5H), 3.24 (t, $J = 11.5$ Hz, 2H), 2.88 (d, $J = 10.5$ Hz, 2H), 2.65-2.73 (m, 1H), 2.64 (s, 3H), 2.36 (brs, 1H), 1.99 (t, $J = 11.0$ Hz, 2H), 1.72 (d, $J = 11.0$ Hz, 2H), 1.62 (d, $J = 12.0$ Hz, 2H), 1.53 (q, $J = 10.0$ Hz, 2H), 1.37 (q, $J = 8.5$ Hz, 2H).
终产物 222	C1		MS (ESI ⁺) $m/z = 557.35$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (s, 1H), 8.75 (s, 1H), 8.60 (s, 2H), 8.50 (s, 1H), 8.17 (s, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.42 (s, 1H), 6.98 (s, 1H), 6.59-6.65 (m, 1H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.5$ Hz,

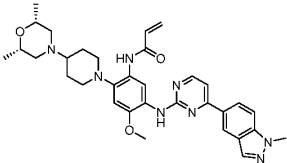
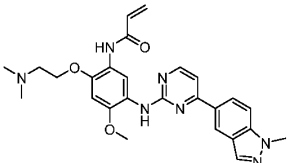
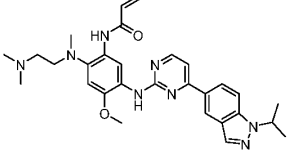
			1H), 4.09 (s, 3H), 3.84 (s, 3H), 3.62 (s, 1H), 3.39 (t, $J = 5.5$ Hz, 2H), 3.21 (s, 3H), 2.57-2.60 (m, 6H), 2.46 (s, 3H), 1.87-1.91 (m, 1H), 1.68-1.72 (m, 1H).
终产物 223	C2		MS (ESI ⁺) $m/z = 557.37$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (s, 1H), 8.82 (s, 1H), 8.65 (s, 1H), 8.62 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.51 (s, 1H), 6.98 (s, 1H), 6.60-6.65 (m, 1H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 11.0$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.62 (s, 1H), 3.39 (t, $J = 6.0$ Hz, 2H), 3.21 (s, 3H), 2.54-2.61 (m, 6H), 2.46-2.50 (m, 3H), 1.70-1.73 (m, 1H), 1.88-1.90 (m, 1H).
终产物 224	C1		MS (ESI ⁺) $m/z = 571.33$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.13 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.50 (s, 2H), 8.17 (s, 1H), 8.08 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.42 (s, 1H), 6.93 (s, 1H), 6.63-6.66 (m 1H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.72 (d, $J = 10.0$ Hz, 1H), 4.09 (s, 3H), 3.84 (s, 3H), 3.38 (t, $J = 5.5$ Hz, 2H), 3.21 (s, 3H), 2.85 (d, $J = 11.0$ Hz, 2H), 2.64-2.69 (m, 1H), 2.63 (s, 3H), 2.40 (t, $J = 6.0$ Hz, 2H), 1.85 (t, $J = 11.5$ Hz, 2H), 1.67 (d, $J = 11.0$ Hz, 2H), 1.53-1.56 (m, 2H).
终产物 225	C2		MS (ESI ⁺) $m/z = 571.31$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.51 (s,

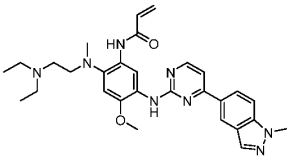
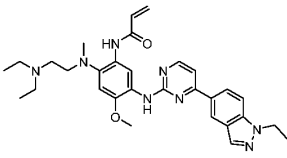
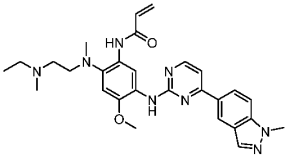
			1H), 8.31 (d, $J = 20.8$ Hz, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.49 (s, 1H), 6.93 (s, 1H), 6.61-6.64 (m, 1H), 6.23 (d, $J = 17.0$ Hz, 1H), 5.72 (d, $J = 11.0$ Hz, 1H), 4.13 (s, 3H), 3.85 (s, 3H), 3.38 (t, $J = 6.0$ Hz, 2H), 3.21 (s, 3H), 2.85 (d, $J = 11.0$ Hz, 2H), 2.65-2.70 (m, 1H), 2.64 (s, 3H), 2.40 (t, $J = 6.0$ Hz, 2H), 1.85 (t, $J = 11.0$ Hz, 2H), 1.68 (d, $J = 10.5$ Hz, 2H), 1.54-1.57 (m, 2H).
终产物 226	C1		MS (ESI ⁺) $m/z = 541.33$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 8.75 (s, 1H), 8.61 (s, 1H), 8.50 (s, 2H), 8.18 (s, 1H), 8.08 (d, $J = 8.9$ Hz, 1H), 7.76 (d, $J = 8.9$ Hz, 1H), 7.43 (s, 1H), 6.93 (s, 1H), 6.61-6.66 (m, 1H), 6.24 (d, $J = 17.2$ Hz, 1H), 5.73 (d, $J = 10.6$ Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 2.85 (d, $J = 11.0$ Hz, 2H), 2.68-2.70 (m, 1H), 2.64 (s, 3H), 2.25 (q, $J = 7.0$ Hz, 2H), 1.68-1.77 (m, 4H), 1.54-1.59 (m, 2H), 0.96 (t, $J = 7.1$ Hz, 3H).
终产物 227	C2		MS (ESI ⁺) $m/z = 541.28$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 8.85 (s, 2H), 8.66 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.54 (s, 1H), 6.99 (s, 1H), 6.65-6.70 (m, 1H), 6.25 (dd, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.5$ Hz, 1H), 4.14 (s, 3H), 3.87 (s, 3H), 3.44 (brs, 1H), 2.83-3.15 (m, 5H), 2.67 (s, 4H),

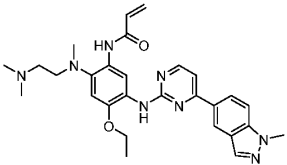
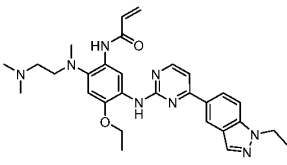
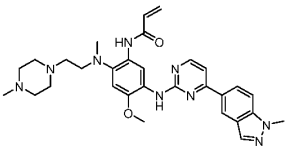
			1.84-1.94 (m, 4H), 1.23 (s, 3H).
终产物 228	C3		MS (ESI ⁺) m/z = 499.20 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.97 (s, 1H), 8.87 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 5.0 Hz, 1H), 6.90 (s, 1H), 6.65-6.71 (m, 1H), 6.33 (d, J = 16.5 Hz, 1H), 5.81 (d, J = 10.5 Hz, 1H), 4.10 (s, 3H), 3.90 (s, 3H), 2.88 (t, J = 4.5 Hz, 4H), 2.56 (brs, 4H), 2.28 (s, 3H).
终产物 229	C3		MS (ESI ⁺) m/z = 527.22 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.99 (s, 1H), 8.88 (s, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.29 (d, J = 8.5 Hz, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.49 (d, J = 5.0 Hz, 1H), 6.87 (s, 1H), 6.64-6.70 (m, 1H), 6.33 (d, J = 17.0 Hz, 1H), 5.81 (d, J = 10.0 Hz, 1H), 4.10 (s, 3H), 3.90 (s, 3H), 2.85 (d, J = 10.5 Hz, 2H), 2.54-2.56 (m, 2H), 2.45 (brs, 2H), 2.24 (s, 3H), 1.04 (d, J = 6.0 Hz, 6H).
终产物 230	C3		MS (ESI ⁺) m/z = 582.23 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 2H), 8.88 (s, 1H), 8.47-8.48 (d, J = 4.0 Hz, 1H), 8.29 (d, J = 7.2 Hz, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 4.4 Hz, 1H), 6.87 (s, 1H), 6.72-6.77 (m, 1H), 6.33 (d, J = 13.6 Hz, 1H), 5.80 (d, J = 8.0 Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.03 (d, J = 8.4 Hz,

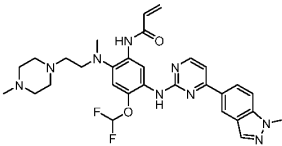
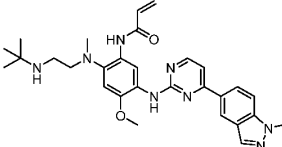
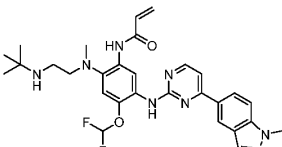
			2H), 2.69 (t, $J = 8.8$ Hz, 2H), 2.54 (brs, 4H), 2.29-2.34 (m, 5H), 2.17 (s, 3H), 1.85 (d, $J = 8.4$ Hz, 2H), 1.70-1.75 (m, 2H).
终产物 231	C3		MS (ESI ⁺) $m/z = 527.13$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (s, 1H), 9.13 (s, 1H), 8.91 (s, 1H), 8.50 (d, $J = 5.5$ Hz, 1H), 8.31 (d, $J = 8.5$ Hz, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 7.72 (d, $J = 9.0$ Hz, 1H), 7.50 (d, $J = 5.0$ Hz, 1H), 6.96 (s, 1H), 6.67-6.73 (m, 1H), 6.34 (d, $J = 17.0$ Hz, 1H), 5.80 (d, $J = 10.0$ Hz, 1H), 4.10 (s, 3H), 3.89 (s, 3H), 2.80 (brs, 2H), 2.72 (brs, 1H), 2.65 (s, 3H), 2.17 (s, 3H), 1.89 (brs, 2H), 1.72 (d, $J = 11.5$ Hz, 2H), 1.55-1.62 (m, 2H).
终产物 232	C3		MS (ESI ⁺) $m/z = 543.17$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.98 (s, 1H), 8.87 (s, 1H), 8.48 (d, $J = 5.5$ Hz, 1H), 8.28 (dd, $J = 8.5, 1.0$ Hz, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.71 (d, $J = 9.0$ Hz, 1H), 7.48 (d, $J = 5.5$ Hz, 1H), 6.91 (s, 1H), 6.65-6.71 (m, 1H), 6.33 (d, $J = 17.0$ Hz, 1H), 5.80 (d, $J = 10.0$ Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.48 (brs, 2H), 3.26 (s, 3H), 2.87 (brs, 4H), 2.51-2.64 (m, 6H).
终产物 233	C3		MS (ESI ⁺) $m/z = 610.25$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.98 (s, 1H), 8.87 (s, 1H), 8.48 (d, $J = 5.0$ Hz, 1H), 8.29 (d, $J = 9.0$ Hz, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.71 (d, $J = 9.0$ Hz, 1H), 7.48 (d, $J = 5.5$ Hz, 1H), 6.86 (s,

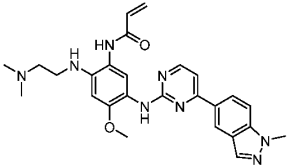
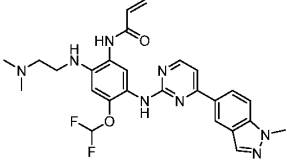
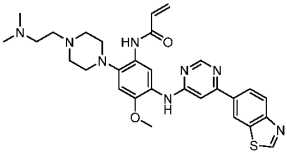
			1H), 6.72-6.77 (m, 1H), 6.33 (d, $J = 17.0$ Hz, 1H), 5.80 (d, $J = 10.5$ Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.03 (d, $J = 10.5$ Hz, 2H), 2.80 (s, 2H), 2.67 (t, $J = 11.0$ Hz, 2H), 2.50-2.49 (m, 1H), 2.10-2.22 (m, 5H), 1.83-1.97 (m, 4H), 1.69-1.72 (m, 2H), 1.00 (brs, 6H).
终产物 234	C3		收率: 24.03%. MS (ESI ⁺) $m/z = 610.20$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.98 (s, 1H), 8.87 (s, 1H), 8.47 (d, $J = 5.0$ Hz, 1H), 8.28 (d, $J = 9.0$ Hz, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.71 (d, $J = 8.5$ Hz, 1H), 7.48 (d, $J = 4.5$ Hz, 1H), 6.87 (s, 1H), 6.69-6.75 (m, 1H), 6.33 (d, $J = 16.5$ Hz, 1H), 5.80 (d, $J = 10.0$ Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.41 (brs, 2H), 2.97-3.06 (m, 6H), 2.63-2.70 (m, 6H), 1.85 (brs, 2H), 1.73 (brs, 2H), 1.23-1.27 (m, 6H).
终产物 235	C3		MS (ESI ⁺) $m/z = 569.20$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 1H), 8.98 (s, 1H), 8.87 (s, 1H), 8.48 (d, $J = 5.0$ Hz, 1H), 8.28 (d, $J = 9.0$ Hz, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.71 (d, $J = 9.0$ Hz, 1H), 7.47 (d, $J = 5.0$ Hz, 1H), 6.92 (s, 1H), 6.65-6.71 (m, 1H), 6.32 (d, $J = 17.0$ Hz, 1H), 5.79 (d, $J = 10.0$ Hz, 1H), 4.09 (s, 3H), 3.89-3.92 (m, 5H), 3.28-3.30 (m, 2H), 2.87 (s, 4H), 2.70 (s, 4H), 2.42-2.44 (m, 1H), 1.76 (d, $J = 12.0$ Hz, 2H), 1.41-1.48 (m, 2H).

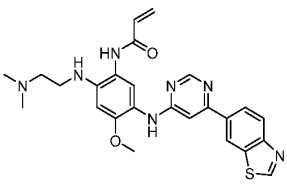
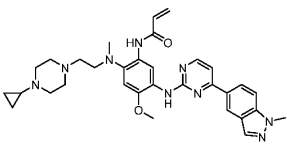
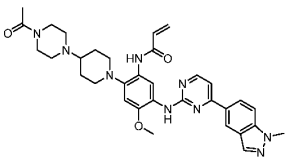
终产物 236	C3		收率: 34%. MS (ESI ⁺) m/z = 597.32 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 2H), 8.87 (s, 1H), 8.48 (d, <i>J</i> = 5.2 Hz, 1H), 8.28 (d, <i>J</i> = 8.8, 1.2 Hz, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.71 (d, <i>J</i> = 9.2 Hz, 1H), 7.48 (d, <i>J</i> = 5.2 Hz, 1H), 6.87 (s, 1H), 6.70-6.73 (m, 1H), 6.33 (d, <i>J</i> = 16.8 Hz, 1H), 5.80 (d, <i>J</i> = 10.8 Hz, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.53-3.57 (m, 2H), 3.04 (d, <i>J</i> = 11.6 Hz, 2H), 2.82 (d, <i>J</i> = 10.4 Hz, 2H), 2.68 (t, <i>J</i> = 10.8 Hz, 2H), 2.20-2.30 (m, 1H), 1.70-1.87 (m, 6H), 1.07 (d, <i>J</i> = 6.4 Hz, 6H).
终产物 237	C3		MS (ESI ⁺) m/z = 488.15 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.79 (s, 1H), 8.98 (s, 1H), 8.84 (s, 1H), 8.47 (d, <i>J</i> = 5.5 Hz, 1H), 8.28 (d, <i>J</i> = 9.0 Hz, 1H), 8.14 (s, 1H), 8.01 (s, 1H), 7.71 (d, <i>J</i> = 9.0 Hz, 1H), 7.46 (d, <i>J</i> = 5.0 Hz, 1H), 6.95 (s, 1H), 6.48-6.54 (m, 1H), 6.32 (dd, <i>J</i> = 17.0, 1.5 Hz, 1H), 5.79 (dd, <i>J</i> = 11.5, 1.5 Hz, 1H), 4.18 (t, <i>J</i> = 5.5 Hz, 2H), 4.09 (s, 3H), 3.88 (s, 3H), 2.58 (t, <i>J</i> = 5.0 Hz, 2H), 2.28 (s, 6H).
终产物 238	C21		MS (ESI ⁺) m/z = 529.14 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.14 (s, 1H), 9.28 (s, 1H), 8.93 (s, 1H), 8.50 (d, <i>J</i> = 5.5 Hz, 1H), 8.28 (dd, <i>J</i> = 9.0, 1.5 Hz, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.78 (d, <i>J</i> = 9.0 Hz, 1H), 7.49 (d, <i>J</i> = 5.5 Hz, 1H), 7.04 (s, 1H), 6.51 (brs, 1H), 6.36 (dd, <i>J</i> = 17.0, 1.5 Hz, 1H), 5.83 (dd, <i>J</i> = 10.5, 2.0

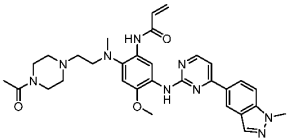
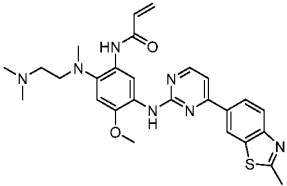
			Hz, 1H), 5.02-5.08 (m, 1H), 3.90 (s, 3H), 2.92 (brs, 2H), 2.71 (s, 3H), 2.26 (brs, 8H), 1.51 (d, $J = 6.5$ Hz, 6H).
终产物 239	C3		MS (ESI ⁺) $m/z = 529.19$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.78 (s, 1H), 9.22 (s, 1H), 8.91 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.30 (d, $J = 8.0$ Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.72 (d, $J = 8.8$ Hz, 1H), 7.49 (d, $J = 5.1$ Hz, 1H), 7.00 (s, 1H), 6.53 (s, 1H), 6.34 (dd, $J = 16.8, 1.5$ Hz, 1H), 5.82 (d, $J = 11.0$ Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.26-2.99 (m, 2H), 2.87 (s, 1H), 2.64-2.70 (m, 3H), 2.46-2.60 (m, 5H), 1.26-1.08 (m, 2H), 0.96 (brs, 4H).
终产物 240	C29		MS (ESI ⁺) $m/z = 543.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.78 (s, 1H), 9.23 (s, 1H), 8.91 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.28 (d, $J = 8.8$ Hz, 1H), 8.15 (s, 1H), 7.88 (s, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.45 (d, $J = 5.2$ Hz, 1H), 7.00 (s, 1H), 6.58 (s, 1H), 6.35 (d, $J = 16.9$ Hz, 1H), 5.82 (d, $J = 11.6$ Hz, 1H), 4.48 (q, $J = 7.2$ Hz, 2H), 3.93 (s, 3H), 3.06 (s, 4H), 2.87 (s, 2H), 2.71 (s, 3H), 2.51-2.60 (m, 2H), 1.43 (t, $J = 7.1$ Hz, 3H), 1.03-1.07 (m, 6H).
终产物 241	C3		MS (ESI ⁺) $m/z = 515.18$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 9.23 (s, 1H), 8.90 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.30 (d, $J = 8.8$ Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.72 (d, $J = 8.8$

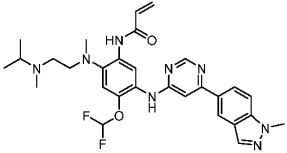
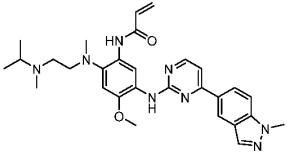
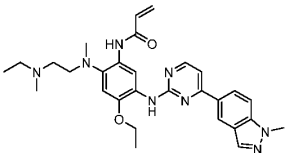
			Hz, 1H), 7.49 (d, $J = 5.3$ Hz, 1H), 7.02 (s, 1H), 6.49-6.53 (m, 1H), 6.35 (d, $J = 16.7$ Hz, 1H), 5.82 (d, $J = 11.7$ Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 2.85-2.98 (m, 2H), 2.69 (s, 4H), 2.31-2.49 (m, 3H), 2.21 (brs, 3H), 1.05 (brs, 3H).
终产物 242	C30		MS (ESI ⁺) $m/z = 515.14$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.14 (s, 1H), 9.33 (s, 1H), 8.96 (s, 1H), 8.50 (d, $J = 5.0$ Hz, 1H), 8.33 (d, $J = 8.5$ Hz, 1H), 8.14 (s, 1H), 7.97 (s, 1H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.51 (d, $J = 5.0$ Hz, 1H), 7.03 (s, 1H), 6.46-6.48 (m, 1H), 6.36 (d, $J = 16.5$ Hz, 1H), 5.82 (d, $J = 11.0$ Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 4.09 (s, 3H), 2.90 (s, 2H), 2.69 (s, 3H), 2.23-2.40 (m, 8H), 1.39 (t, $J = 6.5$ Hz, 3H),
终产物 243	C22		MS (ESI ⁺) $m/z = 529.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.18 (s, 1H), 9.36 (s, 1H), 8.97 (s, 1H), 8.50 (d, $J = 5.0$ Hz, 1H), 8.30 (d, $J = 9.0$ Hz, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.50 (d, $J = 5.0$ Hz, 1H), 7.03 (s, 1H), 6.43-6.49 (m, 1H), 6.36 (d, $J = 16.5$ Hz, 1H), 5.83 (d, $J = 10.0$ Hz, 1H), 4.49 (q, $J = 7.0$ Hz, 2H), 4.15 (q, $J = 7.0$ Hz, 2H), 2.87 (s, 2H), 2.70 (s, 3H), 2.27 (s, 2H), 2.20 (s, 6H), 1.37-1.44 (m, 6H)
终产物 244	C3		MS (ESI ⁺) $m/z = 556.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.38 (s, 1H), 9.12 (s, 1H), 8.90 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.30 (d, $J = 8.9$ Hz, 1H),

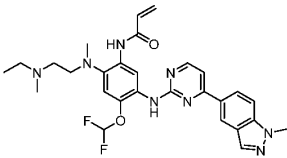
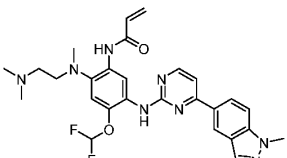
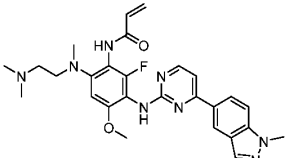
			8.14 (s, 1H), 8.00 (s, 1H), 7.71 (d, $J = 8.9$ Hz, 1H), 7.49 (d, $J = 5.3$ Hz, 1H), 6.99 (s, 1H), 6.64-6.69 (m, 1H), 6.34 (dd, $J = 17.1, 1.0$ Hz, 1H), 5.82 (d, $J = 10.7$ Hz, 1H), 4.09 (s, 3H), 3.89 (s, 3H), 2.97 (t, $J = 6.3$ Hz, 2H), 2.69 (s, 3H), 2.35 (brs, 10H), 2.15 (s, 3H).
终产物 245	C27		MS (ESI ⁺) $m/z = 592.11$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.46 (s, 1H), 8.89 (s, 1H), 8.79 (s, 1H), 8.48 (d, $J = 5.6$ Hz, 1H), 8.45 (s, 1H), 8.26 (d, $J = 8.9$ Hz, 1H), 8.14 (s, 1H), 7.72 (d, $J = 8.9$ Hz, 1H), 7.49 (d, $J = 5.3$ Hz, 1H), 6.94-7.31 (m, 2H), 6.65-6.72 (m, 1H), 6.33 (d, $J = 16.9$ Hz, 1H), 5.83 (d, $J = 11.2$ Hz, 1H), 4.09 (s, 3H), 2.97 (t, $J = 6.2$ Hz, 2H), 2.69 (s, 3H), 2.37-2.39 (m, 10H), 2.16 (s, 3H).
终产物 246	C3		MS (ESI ⁺) $m/z = 529.08$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.48 (s, 1H), 9.17 (s, 1H), 8.90 (s, 1H), 8.49 (d, $J = 5.0$ Hz, 1H), 8.30 (d, $J = 9.0$ Hz, 1H), 8.13 (s, 1H), 8.00 (s, 1H), 7.71 (d, $J = 9.0$ Hz, 1H), 7.49 (d, $J = 5.5$ Hz, 1H), 6.96 (s, 1H), 6.69-6.75 (m, 1H), 6.33 (d, $J = 17.0$ Hz, 1H), 5.79 (d, $J = 10.5$ Hz, 1H), 4.09 (s, 3H), 3.89 (s, 3H), 2.89 (s, 2H), 2.67 (s, 3H), 2.61 (s, 2H), 1.05 (s, 9H).
终产物 247	C27		收率: 11.30%. MS (ESI ⁺) $m/z = 565.22$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.82 (s, 1H), 8.86 (s, 1H), 8.75 (s, 2H), 8.51 (s, 1H), 8.47 (d, $J = 5.0$ Hz, 1H),

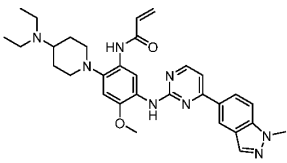
			8.24 (d, $J = 9.0$ Hz, 1H), 8.13 (s, 1H), 7.72 (d, $J = 9.0$ Hz, 1H), 7.49 (d, $J = 5.0$ Hz, 1H), 7.01-7.31 (m, 3H), 6.32 (d, $J = 17.0$ Hz, 1H), 5.81 (d, $J = 11.0$ Hz, 1H), 4.09 (s, 3H), 3.23 (s, 2H), 3.05 (s, 2H), 2.62 (s, 3H), 1.30 (s, 9H).
终产物 248	C3		MS (ESI ⁺) $m/z = 529.21$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.41 (s, 1H), 8.67 (s, 1H), 8.40 (d, $J = 5.1$ Hz, 1H), 8.21 (d, $J = 8.9$ Hz, 1H), 8.15 (s, 1H), 7.92 (s, 2H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.37 (d, $J = 5.1$ Hz, 1H), 6.48-6.54 (m, 1H), 6.43 (s, 1H), 6.26 (d, $J = 17.2$ Hz, 1H), 5.74 (d, $J = 10.2$ Hz, 1H), 4.76 (s, 1H), 4.08 (s, 3H), 3.86 (s, 3H), 3.18 (d, $J = 5.6$ Hz, 2H), 2.49-2.50 (m, 2H), 2.20 (s, 6H).
终产物 249	C27		MS (ESI ⁺) $m/z = 523.29$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.50 (s, 1H), 8.62 (s, 1H), 8.40 (s, 1H), 8.38 (t, $J = 5.2$ Hz, 1H), 8.19 (s, 1H), 8.16 (s, 1H), 7.73 (s, 1H), 7.70 (s, 1H), 7.37 (d, $J = 5.2$ Hz, 1H), 6.90-7.27 (m, 1H), 6.53 (s, 1H), 6.47-6.51 (m, 1H), 6.25 (d, $J = 17.6$ Hz, 1H), 5.76 (d, $J = 10.4$ Hz, 1H), 5.04 (s, 1H), 4.08 (s, 3H), 3.15 (q, $J = 5.6$ Hz, 2H), 2.49 (s, 2H), 2.20 (s, 6H).
终产物 250	C8		MS (ESI ⁺) $m/z = 559.11$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.49 (s, 1H), 9.04 (s, 1H), 8.89 (s, 1H), 8.86 (s, 1H), 8.63 (s, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 7.43 (s, 1H), 6.89 (s,

			1H), 6.60-6.65 (m, 1H), 6.25 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.0$ Hz, 1H), 3.85 (s, 3H), 2.87 (brs, 4H), 2.62 (brs, 4H), 2.45-2.48 (m, 2H), 2.37 (t, $J = 6.0$ Hz, 2H), 2.16 (s, 6H).
终产物 251	C8		MS (ESI ⁺) $m/z = 490.26$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.48 (s, 1H), 9.46 (s, 1H), 8.86 (s, 1H), 8.70 (s, 1H), 8.57 (s, 1H), 8.13-8.18 (m, 2H), 7.46 (s, 1H), 7.19 (s, 1H), 6.45-6.51 (m, 1H), 6.42 (s, 1H), 6.24 (d, $J = 17.0, 1.5$ Hz, 1H), 5.72 (d, $J = 10.5, 2.0$ Hz, 1H), 4.94 (s, 1H), 3.82 (s, 3H), 3.20 (q, $J = 6.0$ Hz, 2H), 2.49-2.50 (m, 2H), 2.20 (s, 6H).
终产物 252	C3		MS (ESI ⁺) $m/z = 582.34$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.40 (s, 1H), 9.13 (s, 1H), 8.90 (s, 1H), 8.49 (d, $J = 5.5$ Hz, 1H), 8.30 (d, $J = 8.9$ Hz, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.71 (d, $J = 8.9$ Hz, 1H), 7.49 (d, $J = 5.2$ Hz, 1H), 7.00 (s, 1H), 6.64-6.70 (m, 1H), 6.35 (d, $J = 17.0$ Hz, 1H), 5.82 (d, $J = 10.3$ Hz, 1H), 4.09 (s, 3H), 3.89 (s, 3H), 2.97 (t, $J = 6.2$ Hz, 2H), 2.69 (s, 3H), 2.42-2.50 (m, 4H), 2.32-2.35 (m, 6H), 1.55-1.57 (m, 1H), 0.38 (d, $J = 4.5$ Hz, 2H), 0.25 (s, 2H).
终产物 253	C3		MS (ESI ⁺) $m/z = 610.31$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.72 (s, 1H), 9.12 (s, 1H), 8.90 (s, 2H), 8.50 (d, $J = 5.5$ Hz, 1H), 8.31 (d, $J = 9.0$ Hz, 1H), 8.18 (s, 1H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.58 (d, $J = 5.5$ Hz, 1H), 6.90 (s, 1H),

			6.69-6.74 (m, 1H), 6.34 (d, $J = 17.0$ Hz, 1H), 5.81 (d, $J = 10.0$ Hz, 1H), 4.53 (d, $J = 13.0$ Hz, 2H), 4.10 (s, 3H), 4.06 (s, 1H), 3.90 (s, 3H), 3.52 (d, $J = 9.0$ Hz, 2H), 3.46 (t, $J = 12.5$ Hz, 1H), 3.37 (s, 1H), 3.19 (t, $J = 11.5$ Hz, 3H), 2.96-3.05 (m, 2H), 2.78 (brs, 2H), 2.35 (s, 5H), 2.13 (d, $J = 10.0$ Hz, 2H), 2.07 (s, 3H), 1.96-1.99 (m, 2H).
终产物 254	C3		MS (ESI ⁺) $m/z = 584.30$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (s, 1H), 9.10 (s, 1H), 8.90 (s, 1H), 8.49 (d, $J = 5.0$ Hz, 1H), 8.31 (d, $J = 9.0$ Hz, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.71 (d, $J = 8.5$ Hz, 1H), 7.49 (d, $J = 5.0$ Hz, 1H), 6.99 (s, 1H), 6.63-6.69 (m, 1H), 6.36 (d, $J = 17.0$ Hz, 1H), 5.81 (d, $J = 10.5$ Hz, 1H), 4.09 (s, 3H), 3.89 (s, 3H), 3.32-3.40 (m, 4H), 3.01 (t, $J = 6.5$ Hz, 2H), 2.70 (s, 3H), 2.28-2.41 (m, 6H), 1.95 (s, 3H).
终产物 255	C13		MS (ESI ⁺) $m/z = 518.21$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.18 (s, 1H), 9.36 (s, 1H), 9.27 (s, 1H), 8.55 (d, $J = 5.2$ Hz, 1H), 8.35 (dd, $J = 8.6, 1.4$ Hz, 1H), 8.03 (s, 1H), 7.98 (s, $J = 8.4$ Hz, 1H), 7.54 (d, $J = 5.2$ Hz, 1H), 7.06 (s, 1H), 6.47 (d, $J = 5.6$ Hz, 2H), 5.84 (t, $J = 6.4$ Hz, 1H), 3.89 (s, 3H), 2.90 (s, 2H), 2.84 (s, 3H), 2.71 (s, 3H), 2.28-2.33 (m, 2H), 2.24 (s, 6H).

终产物 256	C11		MS (ESI ⁺) m/z = 565.22 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.94 (s, 1H), 9.21 (s, 1H), 8.67 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 10.8 Hz, 1H), 6.92-7.29 (m, 2H), 6.40-6.47 (m, 1H), 6.30 (d, J = 17.2 Hz, 1H), 5.82 (d, J = 12.0 Hz, 1H), 4.08 (s, 3H), 2.79-2.87 (m, 3H), 2.71 (s, 3H), 2.44-2.47 (m, 2H), 2.20 (s, 3H), 0.98 (s, d, J = 6.4 Hz, 6H).
终产物 257	C3		MS (ESI ⁺) m/z = 529.27 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.84 (s, 2H), 8.83-8.88 (m, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 8.03 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 5.2 Hz, 1H), 7.05 (brs, 1H), 6.98 (s, 1H), 6.33 (d, J = 16.8 Hz, 1H), 5.81 (d, J = 10.8 Hz, 1H), 4.09 (s, 3H), 3.92 (s, 3H), 3.32-3.47 (m, 1H), 2.84-3.05 (m, 2H), 2.62-2.68 (m, 6H), 2.33 (brs, 1H), 2.24 (brs, 1H), 0.98-1.23 (m, 6H).
终产物 258	C30		MS (ESI ⁺) m/z = 529.18 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (brs, 1H), 9.30 (brs, 1H), 8.93 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.32 (d, J = 8.8 Hz, 1H), 8.14 (s, 1H), 7.96 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 5.2 Hz, 1H), 7.01 (s, 1H), 6.50-6.55 (m, 1H), 6.37 (d, J = 15.6 Hz, 1H), 5.83 (d, J = 11.6 Hz, 1H), 4.18 (q, J = 6.8 Hz, 2H), 4.09 (s, 3H), 2.89

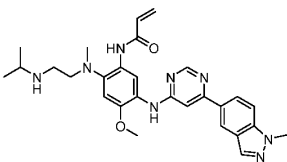
			(brs, 2H), 2.68 (s, 3H), 2.19-2.45 (m, 7H), 1.39 (t, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 6.0$ Hz, 3H).
终产物 259	C27		MS (ESI ⁺) $m/z = 551.27$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.03 (s, 1H), 9.06 (s, 1H), 8.79 (s, 1H), 8.45-8.48 (m, 2H), 8.26 (d, $J = 8.8$ Hz, 1H), 8.13 (s, 1H), 7.72 (d, $J = 8.8$ Hz, 1H), 7.49 (d, $J = 6.0$ Hz, 1H), 6.94-7.31 (m, 2H), 6.47-6.55 (m, 1H), 6.33 (d, $J = 16.8$ Hz, 1H), 5.83 (d, $J = 10.0$ Hz, 1H), 4.09 (s, 3H), 2.86 (s, 2H), 2.70 (s, 3H), 2.41 (s, 4H), 2.20 (s, 3H), 1.01-1.04 (m, 3H).
终产物 260	C27		MS (ESI ⁺) $m/z = 537.17$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.26 (s, 1H), 9.10 (s, 1H), 8.81 (s, 1H), 8.46-8.49 (m, 2H), 8.27 (dd, $J = 8.9, 1.3$ Hz, 1H), 8.13 (s, 1H), 7.73 (d, $J = 8.9$ Hz, 1H), 7.50 (d, $J = 5.3$ Hz, 1H), 6.98-7.28 (m, 2H), 6.44-6.47 (m, 1H), 6.34 (dd, $J = 16.9, 1.7$ Hz, 1H), 5.85 (dd, $J = 10.1, 1.7$ Hz, 1H), 4.10 (s, 3H), 2.87 (t, $J = 5.2$ Hz, 2H), 2.71 (s, 3H), 2.34 (brs, 2H), 2.23 (s, 6H).
终产物 261	C31		MS (ESI ⁺) $m/z = 518.82$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.50 (s, 1H), 8.58 (s, 1H), 8.41 (s, 1H), 8.33 (d, $J = 5.2$ Hz, 1H), 8.19 (s, 1H), 8.14 (d, $J = 8.7$ Hz, 1H), 7.71 (d, $J = 8.7$ Hz, 1H), 7.32 (d, $J = 5.2$ Hz, 1H), 6.56 (s, 1H), 6.48-6.53 (m, 1H), 6.24 (d, $J = 17.2$ Hz, 1H), 5.74 (d, $J = 10.8$ Hz, 1H), 4.08 (s,

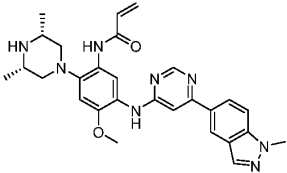
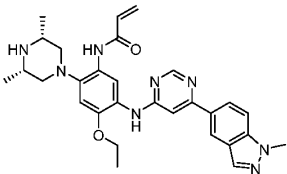
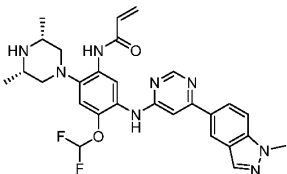
			3H), 3.79 (s, 3H), 3.07 (d, $J = 10.4$ Hz, 2H), 2.78 (s, 3H), 2.49-2.50 (m, 2H), 2.20 (s, 6H).
终产物 262	C3		MS (ESI ⁺) $m/z = 555.23$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.05 (s, 2H), 8.89 (s, 1H), 8.49 (s, 1H), 8.30 (d, $J = 7.7$ Hz, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.49 (s, 1H), 6.89 (s, 1H), 6.73-6.75 (m, 1H), 6.35 (d, $J = 16.3$ Hz, 1H), 5.82 (d, $J = 8.7$ Hz, 1H), 4.10 (s, 3H), 3.89 (s, 3H), 3.06 (brs 3H), 2.75 (brs, 2H), 2.51-2.54 (m, 4H), 1.80 (brs, 4H), 1.04 (brs, 6H).

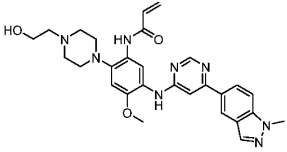
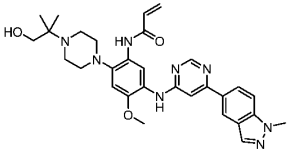
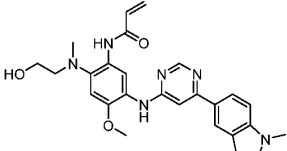
实施例 412-430.

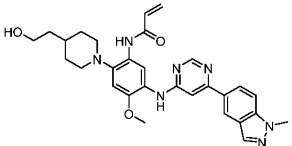
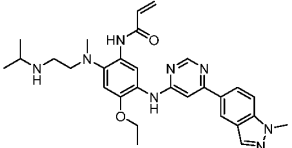
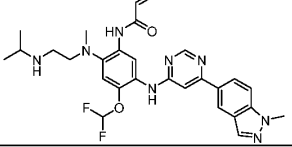
以中间体 C 和市售或实施例 1-69 合成的带有保护基的胺为原料, 运用合成终产物 18 (实施例 167) 的方法制备带有保护基的终产物。氩气保护下, 带有保护基的终产物经 Pd(ppH₃)₄/TES, 以 DCM 或 DCM/MeOH 为溶剂, 室温搅拌脱保护基; 或经酸如 TFA 或 5 HCl, DCM 为溶剂, 室温搅拌脱保护基得终产物 263-281。(表 5)

表 5 终产物 263-281

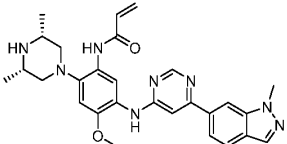
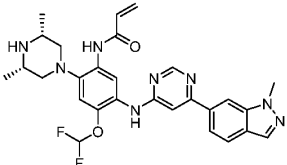
终产物 263	C1		MS (ESI ⁺) $m/z = 515.10$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.73 (s, 1H), 8.74 (s, 1H), 8.61 (s, 1H), 8.59 (s, 1H), 8.48 (s, 1H), 8.16 (s, 1H), 8.07 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.34 (s, 1H), 6.95 (s, 1H), 6.61-6.67 (m, 1H), 6.24 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.72 (dd, $J = 11.5, 1.5$ Hz, 1H), 4.08 (s, 3H), 3.83 (s, 3H), 2.87 (d, $J = 5.0$ Hz, 2H), 2.63-2.75 (m, 6H), 1.90 (brs, 1H),
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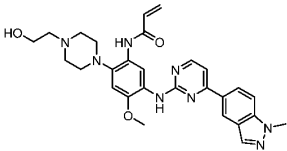
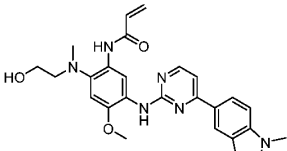
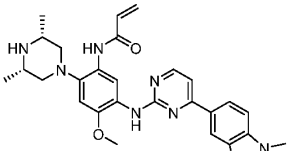
			1.00 (d, $J = 6.0$ Hz, 6H).
终产物 264	C1		MS (ESI ⁺) $m/z = 513.45$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.36 (s, 1H), 6.83 (s, 1H), 6.56-6.62 (m, 1H), 6.22 (d, $J = 17.0$ Hz, 1H), 5.73 (d, $J = 10.5$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.02 (brs, 2H), 2.83-2.85 (d, $J = 10.0$ Hz, 2H), 2.25 (t, $J = 10.0$ Hz, 2H), 2.08 (brs, 1H), 0.97 (d, $J = 8.5$ Hz, 6H).
终产物 265	C10		MS (ESI ⁺) $m/z = 527.21$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.64 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 8.17 (s, 1H), 8.09 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.36 (s, 1H), 6.82 (s, 1H), 6.56-6.63 (m, 1H), 6.23 (d, $J = 16.8$ Hz, 1H), 5.74 (d, $J = 10.8$ Hz, 1H), 4.15-4.10 (m, 2H), 4.08 (s, 3H), 3.02 (brs, 2H), 2.83 (d, $J = 9.6$ Hz, 2H), 2.23 (t, $J = 10.4$ Hz, 2H), 2.07 (brs, 1H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.00 (d, $J = 6.4$ Hz, 6H).
终产物 266	C11		MS (ESI ⁺) $m/z = 549.27$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 9.02 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.75 (d, $J = 9.2$ Hz, 1H), 7.35 (s, 1H), 6.97-7.34 (m, 2H), 6.59-6.66 (m, 1H), 6.24 (dd, $J = 17.2, 1.6$

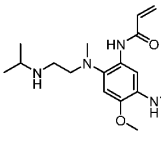
			Hz, 1H), 5.76 (dd, $J = 12.0, 1.6$ Hz, 1H), 4.08 (s, 3H), 3.04 (s, 2H), 2.85 (d, $J = 9.6$ Hz, 2H), 2.20 (t, $J = 10.4$ Hz, 2H), 2.07 (brs, 1H), 0.97 (d, $J = 6.0$ Hz, 6H).
终产物 267	C1		收率: 36.32%. MS (ESI ⁺) $m/z = 529.22$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 8.08 (d, $J = 8.8, 1.2$ Hz, 1H), 7.75 (d, $J = 9.2$ Hz, 1H), 7.38 (s, 1H), 6.88 (s, 1H), 6.58-6.63 (m, 1H), 6.23 (dd, $J = 17.2, 1.6$ Hz, 1H), 5.74 (d, $J = 11.2$ Hz, 1H), 4.41 (t, $J = 5.2$ Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 3.54 (q, $J = 6.0$ Hz, 2H), 2.87 (t, $J = 4.4$ Hz, 4H), 2.64 (brs, 4H), 2.46-2.50 (m, 2H).
终产物 268	C1		MS (ESI ⁺) $m/z = 557.29$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.04 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.08 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.38 (s, 1H), 6.89 (s, 1H), 6.61-6.66 (m, 1H), 6.24 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.75 (d, $J = 11.2$ Hz, 1H), 4.25 (d, $J = 5.0$ Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 3.33 (s, 2H), 2.86 (d, $J = 4.5$ Hz, 4H), 2.76 (brs, 4H), 1.00 (s, 6H).
终产物 269	C1		MS (ESI ⁺) $m/z = 474.23$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.64 (s, 1H), 8.75 (s, 1H), 8.71 (s, 1H), 8.58 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 9.0, 1.5$ Hz, 1H), 7.75 (d, $J = 9.0$ Hz,

			1H), 7.32 (s, 1H), 6.95 (s, 1H), 6.49-6.55 (m, 1H), 6.25 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.72 (dd, $J = 10.5, 2.0$ Hz, 1H), 5.34 (dd, $J = 9.5, 4.5$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.61 (q, $J = 5.0$ Hz, 2H), 2.87 (t, $J = 5.0$ Hz, 2H), 2.73 (s, 3H).
终产物 270	C1		MS (ESI ⁺) $m/z = 528.34$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.99 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J = 8.9, 1.2$ Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.36 (s, 1H), 6.86 (s, 1H), 6.62-6.67 (m, 1H), 6.23 (dd, $J = 16.9, 1.0$ Hz, 1H), 5.73 (d, $J = 10.9$ Hz, 1H), 4.37 (t, $J = 5.0$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.50 (t, $J = 5.5$ Hz, 2H), 3.01 (d, $J = 11.2$ Hz, 2H), 2.65 (t, $J = 10.9$ Hz, 2H), 1.75 (d, $J = 11.1$ Hz, 2H), 1.46-1.47 (m, 1H), 1.44 (t, $J = 7.0$ Hz, 4H).
终产物 271	C10		MS (ESI ⁺) $m/z = 529.23$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.73 (s, 1H), 8.65 (s, 1H), 8.60 (s, 2H), 8.51 (s, 1H), 8.16 (s, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.34 (s, 1H), 6.94 (s, 1H), 6.61-6.67 (m, 1H), 6.25 (d, $J = 16.8$ Hz, 1H), 5.72 (d, $J = 10.4$ Hz, 1H), 4.08-4.11 (m, 5H), 2.87 (s, 2H), 2.62-2.74 (m, 6H), 1.94 (brs, 1H), 1.30 (t, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 6.0$ Hz, 6H).
终产物 272	C11		MS (ESI ⁺) $m/z = 551.18$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.92 (s, 1H), 9.03 (s, 1H), 8.64 (s, 1H), 8.60 (s,

			1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 6.93-7.31 (m, 2H), 6.64-6.68 (m, 1H), 6.27 (d, J = 16.8 Hz, 1H), 5.77 (d, J = 9.2 Hz, 1H), 4.09 (s, 3H), 2.86 (brs, 2H), 2.66-2.76 (m, 6H), 2.04 (brs, 1H), 1.02 (d, J = 6.0 Hz, 6H).
终产物 273	C11		MS (ESI ⁺) m/z = 565.27 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.13 (s, 1H), 9.02 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.36 (s, 1H), 6.96-7.33 (m, 2H), 6.61-6.68 (m, 1H), 6.26 (d, J = 17.2 Hz, 1H), 5.77 (d, J = 10.8 Hz, 1H), 4.40 (t, J = 5.2 Hz, 1H), 4.09 (s, 3H), 3.54 (q, J = 6.0 Hz, 2H), 2.86 (brs, 4H), 2.65 (brs, 4H), 2.46-2.48 (m, 2H).
终产物 274	C2		MS (ESI ⁺) m/z = 529.31 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.04 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.10 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 6.88 (s, 1H), 6.59-6.66 (m, 1H), 6.23 (d, J = 17.2 Hz, 1H), 5.74 (d, J = 10.8 Hz, 1H), 4.41 (t, J = 5.2 Hz, 1H), 4.13 (s, 3H), 3.86 (s, 3H), 3.54 (q, J = 6.0 Hz, 2H), 2.87 (d, J = 4.4 Hz, 4H), 2.64 (s, 4H), 2.46-2.49 (m, 2H).
终产物 275	C28		MS (ESI ⁺) m/z = 565.26 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- d_6) δ 9.17 (s, 1H), 9.13 (s, 1H), 8.65 (s, 1H), 8.37 (s,

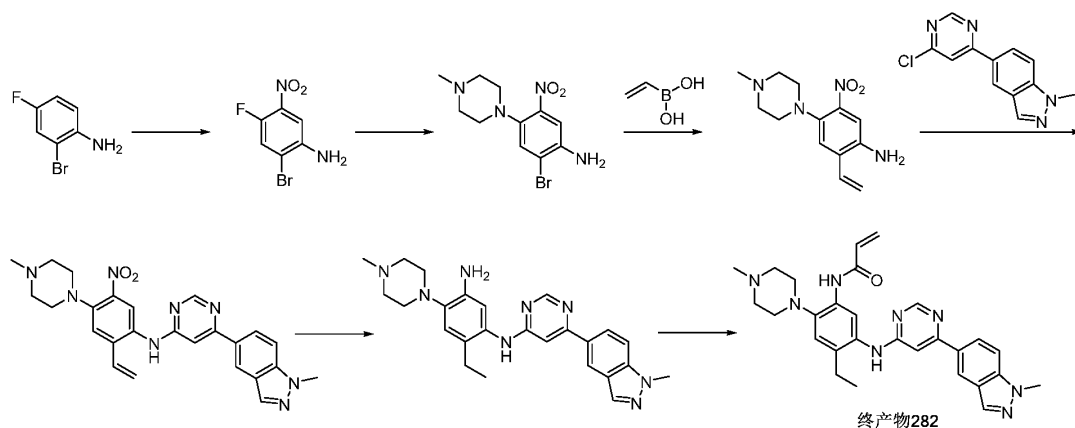
			1H), 8.35 (s, 1H), 8.12 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.46 (s, 1H), 7.01-7.31 (m, 2H), 6.63-6.69 (m, 1H), 6.26 (d, $J = 17.4$ Hz, 1H), 5.78 (d, $J = 10.9$ Hz, 1H), 4.42 (t, $J = 5.5$ Hz, 1H), 4.14 (s, 3H), 3.55 (q, $J = 6.0$ Hz, 2H), 2.86 (brs, 4H), 2.65 (brs, 4H), 2.48 (d, $J = 6.2$ Hz, 2H).
终产物 276	C2		MS (ESI ⁺) $m/z = 513.24$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.06 (s, 1H), 8.83 (s, 1H), 8.65 (s, 1H), 8.41 (s, 1H), 8.35 (s, 1H), 8.12 (s, 1H), 7.89 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.48 (s, 1H), 6.85 (s, 1H), 6.60-6.66 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.76 (d, $J = 10.9$ Hz, 1H), 4.15 (s, 3H), 3.87 (s, 3H), 3.04 (s, 2H), 2.86 (d, $J = 10.2$ Hz, 2H), 2.27 (t, $J = 10.6$ Hz, 2H), 0.99 (d, $J = 6.3$ Hz, 6H).
终产物 277	C28		MS (ESI ⁺) $m/z = 549.31$ [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.15 (s, 1H), 9.11 (s, 1H), 8.65 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.88 (d, $J = 8.8$ Hz, 1H), 7.78 (dd, $J = 8.5, 0.8$ Hz, 1H), 7.44 (s, 1H), 7.35-6.98 (m, 2H), 6.59-6.66 (m, 1H), 6.25 (dd, $J = 17.0, 1.6$ Hz, 1H), 5.78 (d, $J = 11.7$ Hz, 1H), 4.13 (s, 3H), 3.01-3.07 (m, 2H), 2.86 (d, $J = 9.7$ Hz, 2H), 2.19 (t, $J = 10.5$ Hz, 2H), 2.10 (s, 1H), 0.97 (d, $J = 6.3$ Hz, 6H).

终产物 278	C3		MS (ESI⁺) m/z = 529.16 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 8.97 (s, 1H), 8.87 (s, 1H), 8.48 (d, J = 4.0 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 3.5 Hz, 1H), 6.91 (s, 1H), 6.65-6.70 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 5.80 (d, J = 9.4 Hz, 1H), 4.45 (s, 1H), 4.09 (s, 3H), 3.89 (s, 3H), 3.54 (brs, 4H), 2.86 (brs, 4H), 2.64 (brs, 4H).
终产物 279	C3		收率: 73%. MS (ESI⁺) m/z = 474.19 [M+H]⁺. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 9.31 (s, 1H), 8.92 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.13 (s, 1H), 8.00 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 6.97 (s, 1H), 6.56-6.62 (m, 1H), 6.34 (d, J = 16.5 Hz, 1H), 5.78 (d, J = 10.5 Hz, 1H), 5.27 (s, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 3.59 (d, J = 4.5 Hz, 2H), 2.86 (d, J = 4.0 Hz, 2H), 2.72 (s, 3H).
终产物 280	C3		MS (ESI⁺) m/z = 513.30 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.05 (s, 1H), 9.01 (s, 1H), 8.88 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 6.86 (s, 1H), 6.62-6.69 (m, 1H), 6.34 (d, J = 17.6 Hz, 1H), 5.81 (d, J = 10.8 Hz, 1H), 4.09 (s, 3H), 3.89 (s, 3H), 3.03 (brs, 2H), 2.83 (d, J = 10.0 Hz, 2H), 2.26 (t, J = 10.4 Hz, 2H), 2.07 (brs, 1H), 0.98 (d, J = 6.4 Hz,

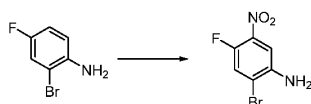
			6H).
终产物 281	C3		收率: 19.41%. MS (ESI ⁺) m/z = 515.22 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.73 (s, 1H), 9.22 (s, 1H), 8.91 (s, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 8.13 (s, 1H), 8.00 (s, 1H), 7.71 (d, <i>J</i> = 4.0 Hz, 1H), 7.48 (s, 1H), 6.97 (s, 1H), 6.70-6.80 (m, 1H), 6.32 (d, <i>J</i> = 15.6 Hz, 1H), 5.79 (s, 1H), 4.09 (s, 3H), 3.88 (s, 3H), 2.88 (s, 2H), 2.61-2.68 (m, 6H), 1.90 (brs, 1H), 1.01 (s, 6H).

实施例 431. 终产物 282 制备

N-(2-(4-甲基哌嗪-1-基)-4-乙基-5-[[6-(1-甲基-1H-咪唑-5-基)嘧啶-4-基]氨基]苯基)丙烯酸
胺 (终产物 282)



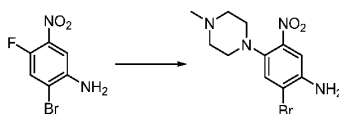
5 第一步: 2-溴-4-氟-5-硝基苯胺



向 250 mL 单口瓶中依次加入 2-溴-4-氟苯胺 (10g, 52.9 mmol) 和浓硫酸 (100 mL),

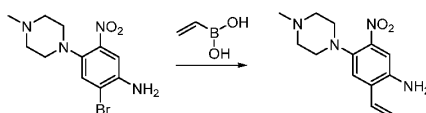
控制温度在 30 °C 搅拌 1 h。降温至 -5 - -10 °C，分批加入硝酸钾 (5.61 g, 55.5 mmol)，加毕，0 °C 反应 2 h，原料反应完全后，将反应液倒入冷的 50% 氢氧化钠水溶液中 (pH>7)，过滤，滤液减压浓缩得到粗品。粗品经柱层析纯化，以 PE/EA=10/1 洗脱，收集产品并减压浓缩，得到 6.0 g 淡黄色固体，收率：48.8%。

5 第二步：2-溴-4-(4-甲基哌嗪-1-基)-5-硝基苯胺



向 100 mL 单口瓶中依次加入 2-溴-4-氟-5-硝基苯胺 (1.0 g, 4.27 mmol)，N-甲基哌嗪 (2.13 g, 21.3 mmol)，DIPEA (2.75 g, 21.3 mmol) 和 NMP (20 mL)，加毕，升温至 120 °C 反应 1.5 h，TLC 监测反应。原料反应完全后，降温至室温，将反应液倒入 100 mL 水中，水相用乙酸乙酯 (100 mL × 2) 萃取 2 次，合并有机相，减压浓缩得粗品。粗品经柱层析纯化，用 DCM/MeOH = 50/1 洗脱，收集产品并减压浓缩，得到 1.4 g 淡红色固体，收率：104.4%。

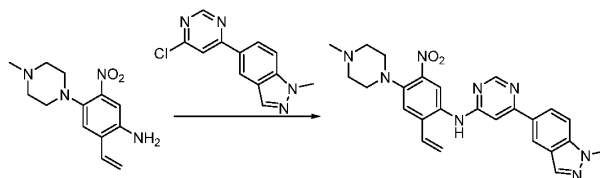
第三步：4-(4-甲基哌嗪-1-基)-5-硝基-2-乙烯基苯胺



氩气保护下，向 100 mL 单口瓶中依次加入 2-溴-4-(4-甲基哌嗪-1-基)-5-硝基苯胺 (1.3 g, 4.14 mmol)，乙烯基硼酸 (956 mg, 6.21 mmol)，醋酸钯 (278 mg, 1.24 mmol)，三苯基膦 (542 mg, 2.07 mmol)，碳酸铯 (13.5 g, 41.4 mmol)，甲苯 (40 mL) 和水 (10 mL)。加毕，升温至 100 °C 搅拌反应 2-3 h。原料反应完全后降温至室温，加入 50 mL 水，用乙酸乙酯 (100 mL × 2) 萃取 2 次，合并有机相，浓缩得粗品。粗品经柱层析纯化，以

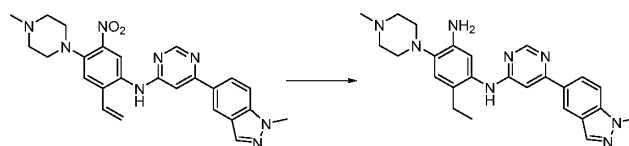
DCM/MeOH = 50/1 洗脱, 收集产品并减压浓缩, 得 490 mg 淡红色油状物, 收率: 45.4%。

第四步: (1-甲基-1H-吡唑-5-基)-N-(4-(4-甲基哌嗪-1-基)-5-硝基-2-乙烯基苯基) 嘧啶-4-胺



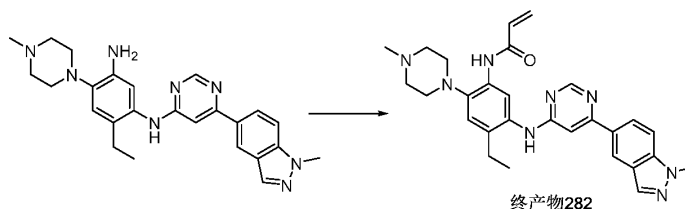
5 以 4-(4-甲基哌嗪-1-基)-5-硝基-2-乙烯基苯胺和中间体 A1 为原料, 制备过程参见实施例 150, 得到 460 mg 淡红色固体, 收率: 55.7%。

第五步: 6-乙基-N1-(6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)-4-(4-甲基哌嗪-1-基)苯-1,3-二胺



10 以 (1-甲基-1H-吡唑-5-基)-N-(4-(4-甲基哌嗪-1-基)-5-硝基-2-乙烯基苯基) 嘧啶-4-胺为原料, 制备过程参见实施例 167 第二步。得到 120 mg 淡红色固体, 收率: 58.4%。

第六步: N-(2-(4-甲基哌嗪-1-基)-4-乙基-5-[(6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基]苯基) 丙烯酰胺

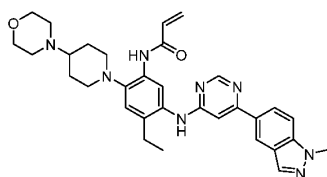


15 以 6-乙基-N1-(6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)-4-(4-甲基哌嗪-1-基)苯-1,3-二胺为原料, 制备过程参见实施例 167 第三步, 得 40 mg 淡黄色固体, 收率: 21.1%。

MS (ESI⁺) $m/z = 497.25$ [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (s, 1H), 8.96 (s, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 8.05 (d, $J = 8.8$ Hz, 1H), 7.96 (s, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 7.09 (d, $J = 9.2$ Hz, 2H), 6.60-6.67 (m, 1H), 6.24 (d, $J = 16.8$ Hz, 1H), 5.75 (d, $J = 10.8$ Hz, 1H), 4.07 (s, 3H), 2.86 (s, 4H), 2.61-2.70 (m, 6H), 2.26 (s, 3H), 1.10 (t, $J = 7.6$ Hz, 3H).

实施例 432. 终产物 283 制备

N-(2-(4-吗啉基哌啶-1-基)-4-乙基-5-{[6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基]氨基}苯基)丙烯酸酰胺 (终产物 283)

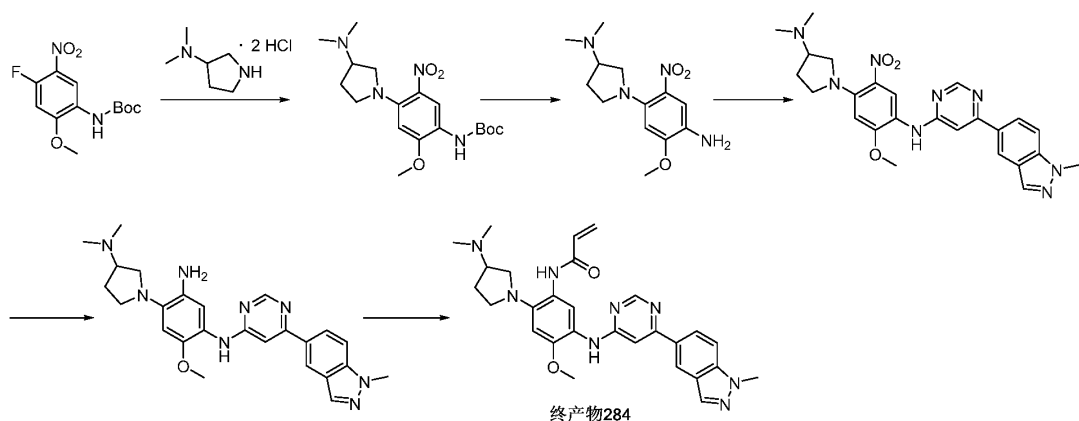


以 2-溴-4-氟-5-硝基苯胺和 4-吗啉基哌啶为原料, 运用合成终产物 282 的方法制备终产物 283。

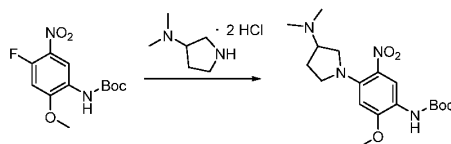
MS (ESI⁺) $m/z = 567.26$ [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.04 (s, 1H), 8.95 (s, 1H), 8.54 (s, 1H), 8.47 (s, 1H), 8.15 (d, $J = 0.4$ Hz, 1H), 8.06 (dd, $J = 1.2, 8.4$ Hz, 1H), 8.00 (s, 1H), 7.73 (d, $J = 6.8$ Hz, 1H), 7.10 (s, 1H), 7.06 (s, 1H), 6.67-6.73 (m, 1H), 6.25 (dd, $J = 1.6, 13.6$ Hz, 1H), 5.75 (dd, $J = 1.2, 9.6$ Hz, 1H), 4.08 (s, 3H), 3.60 (s, 4H), 3.05 (s, 4H), 2.67 (t, $J = 9.2$ Hz, 2H), 2.57-2.60 (m, 2H), 2.57 (s, 2H), 2.27 (t, $J = 8.8$ Hz, 1H), 1.88 (d, $J = 8.4$ Hz, 2H), 1.70-1.76 (m, 2H), 1.10 (t, $J = 6.0$ Hz, 3H).

实施例 433. 终产物 284 制备

N-(2-(4-(3-(二甲基氨基)吡咯烷-1-基)-4-甲氧基-5-{[6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基]氨基}苯基)丙烯酸酰胺 (终产物 284)



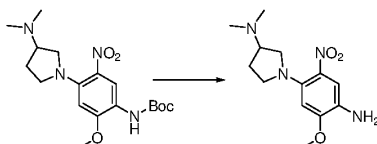
第一步: (4-(3-(二甲基氨基)吡咯烷-1-基)-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯



以 (4-氟-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯和 3-(二甲基氨基)吡咯烷双盐酸盐

5 为原料, 制备过程参见实施例 113 第二步。

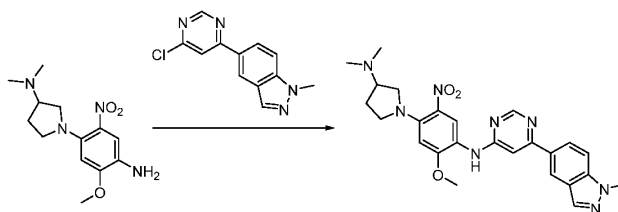
第二步: 1-(4-氨基-5-甲氧基-2-硝基苯基)-N,N-二甲基吡咯烷-3-胺



于 100 mL 单口瓶中依次加入 (4-(3-(二甲基氨基)吡咯烷-1-基)-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯 (210 mg, 1.91 mmol), DCM (10 mL) 和三氟乙酸 (4 mL), 室温搅拌 30 min。反应完全后, 用饱和碳酸氢钠溶液调 pH 至碱性, 用二氯甲烷 (30 mL × 3) 萃取 3 次, 合并有机相, 有机相用饱和食盐水 (30 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 抽滤, 减压浓缩, 粗品经柱层析纯化, 用 DCM/CH₃OH = 30/1 洗脱, 收集产品并减压浓缩, 得 110 mg 红色油状物。

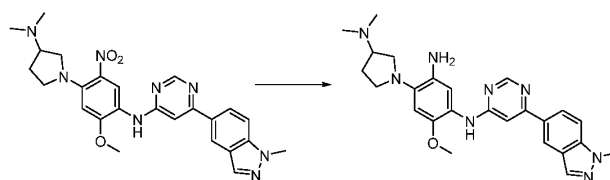
第三步: N-(4-(3-(二甲基氨基)吡咯烷-1-基)-2-甲氧基-5-硝基苯基)-6-(1-甲基-1H-

吡啶-5-基) 嘧啶-4-胺



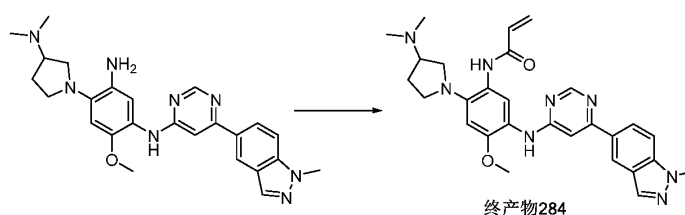
以 1-(4-氨基-5-甲氧基-2-硝基苯基)-N,N-二甲基吡咯烷-3-胺和中间体 A1 为原料, 制备过程参见实施例 150。

5 第四步: (3-(二甲基氨基)吡咯烷-1-基)-6-甲氧基-N1-(6-(1-甲基-1H-吡啶-5-基)嘧啶-4-基)苯-1,3-二胺



以 N-(4-(3-(二甲基氨基)吡咯烷-1-基)-2-甲氧基-5-硝基苯基)-6-(1-甲基-1H-吡啶-5-基)嘧啶-4-胺为原料。制备过程参见实施例 167 第二步。

10 第五步: N-(2-(4-(3-(二甲基氨基)吡咯烷-1-基)-4-甲氧基-5-[[6-(1-甲基-1H-吡啶-5-基)嘧啶-4-基]氨基]苯基)丙烯酰胺



以 (3-(二甲基氨基)吡咯烷-1-基)-6-甲氧基-N1-(6-(1-甲基-1H-吡啶-5-基)嘧啶-4-基)苯-1,3-二胺为原料。制备过程参见实施例 167 第三步。

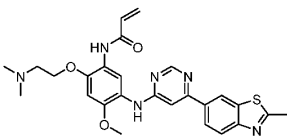
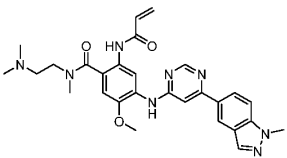
15 MS (ESI⁺) m/z = 513.23 [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 9.41 (s, 1H), 8.64 (s, 1H),

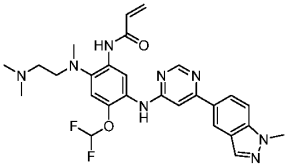
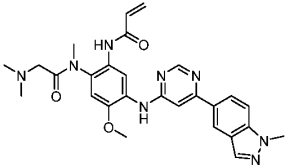
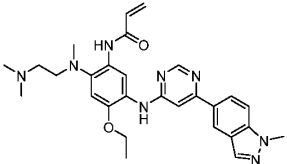
8.55 (s, 1H), 8.46 (s, 1H), 8.16 (s, 1H), 8.06 (d, $J = 9.0$ Hz, 1H), 7.73 (d, $J = 9.0$ Hz, 1H), 7.60 (s, 1H), 7.22 (s, 1H), 6.46-6.52 (m, 2H), 6.21 (d, $J = 18.0$ Hz, 1H), 5.70 (d, $J = 10.0$ Hz, 1H), 4.08 (s, 3H), 3.84 (s, 3H), 3.36-3.41 (m, 1H), 3.20-3.28 (m, 3H), 2.66 (d, $J = 25.6$ Hz, 1H), 2.24 (d, $J = 65.3$ Hz, 6H), 2.08 (d, $J = 5.1$ Hz, 1H), 1.72 (m, 1H).

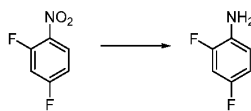
5 实施例 434-439.

以中间体 A 和实施例 83-90 合成的硝基苯胺为原料按照合成终产物 284 方法制备终产物 285-290。(表 6)

表 6 终产物 285-290

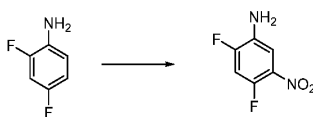
终产物 285	A15		MS (ESI ⁺) $m/z = 505.22$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.69 (s, 1H), 8.82 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.33 (s, 1H), 8.10 (d, $J = 8.6$ Hz, 1H), 8.00 (d, $J = 8.5$ Hz, 1H), 7.29 (s, 1H), 6.94 (s, 1H), 6.45-6.51 (m, 1H), 6.24 (d, $J = 17.0$ Hz, 1H), 5.74 (d, $J = 10.4$ Hz, 1H), 4.19 (t, $J = 5.6$ Hz, 2H), 3.84 (s, 3H), 2.83 (s, 3H), 2.60 (t, $J = 5.6$ Hz, 2H), 2.27 (s, 6H).
终产物 286	A1		MS (ESI ⁺) $m/z = 529.17$ [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.62 (s, 1H), 8.92 (s, 1H), 8.71 (s, 1H), 8.54 (s, 1H), 8.43 (s, 1H), 8.20 (s, 1H), 8.11 (d, $J = 9.0, 1.0$ Hz, 1H), 7.79 (d, $J = 9.0$ Hz, 1H), 7.67 (d, $J = 20.5$ Hz, 1H), 6.95 (s, 1H), 6.51-6.38 (m, 1H), 6.22 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.73 (dd, $J = 10.5, 1.5$ Hz, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.49 (m, 1H), 3.23 (s, 1H), 2.86-2.91 (m, 3H),

			2.34-2.43 (m, 2H), 2.20 (s, 3H), 1.99 (s, 3H).
终产物 287	A1		MS (ESI ⁺) m/z = 537.15 [M+H] ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.24 (s, 1H), 9.05 (s, 1H), 8.71 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 8.09 (dd, <i>J</i> = 9.0, 1.5 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.36 (s, 1H), 6.98-7.27 (m, 2H), 6.40-6.45 (m, 1H), 6.28 (dd, <i>J</i> = 17.0, 2.0 Hz, 1H), 5.80 (dd, <i>J</i> = 10.0, 1.5 Hz, 1H), 4.09 (s, 3H), 2.86 (t, <i>J</i> = 5.5 Hz, 2H), 2.71 (s, 3H), 2.36 (s, 2H), 2.22 (s, 6H).
终产物 288	A1		MS (ESI ⁺) m/z = 514.90 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.55 (s, 1H), 8.87 (s, 1H), 8.69 (s, 1H), 8.53 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 8.10 (d, <i>J</i> = 8.9 Hz, 1H), 7.77 (d, <i>J</i> = 8.8 Hz, 1H), 7.65 (s, 1H), 7.10 (s, 1H), 6.48-6.55 (m, 1H), 6.23 (d, <i>J</i> = 17.1 Hz, 1H), 5.75 (d, <i>J</i> = 10.5 Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.06 (s, 3H), 2.83 (q, <i>J</i> = 15.1 Hz, 2H), 2.15 (s, 6H).
终产物 289	A1		MS (ESI ⁺) m/z = 515.16 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.11 (s, 1H), 8.66 (s, 2H), 8.61 (s, 1H), 8.52 (s, 1H), 8.17 (s, 1H), 8.10 (dd, <i>J</i> = 7.2, 1.2 Hz, 1H), 7.75 (d, <i>J</i> = 7.2 Hz, 1H), 7.38 (s, 1H), 7.01 (s, 1H), 6.38-6.43 (m, 1H), 6.25 (dd, <i>J</i> = 13.6, 1.2 Hz, 1H), 5.75 (d, <i>J</i> = 10.4, 1.2 Hz, 1H), 4.12 (t, <i>J</i> = 5.6 Hz, 2H), 4.09 (s, 3H), 2.88 (s, 2H), 2.71 (s, 3H), 2.33 (s, 2H), 2.22 (s, 6H), 1.31 (t, <i>J</i>



于 100 mL 单口瓶中依次加入 2, 4-二氟-1-硝基苯 (1 g), 甲醇 (10 mL) 和 Pd/C (100 mg), 置换氢气三次, 室温搅拌反应 2-3 h。过滤, 滤液减压浓缩得 810 mg 产品。

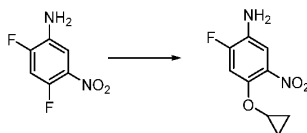
第二步: 2, 4-二氟-5-硝基苯胺



5

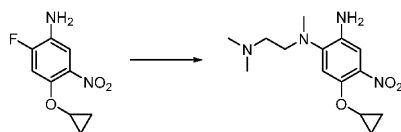
于 100 mL 三口瓶中加入 2, 4-二氟苯胺 (630 mg, 4.88 mmol) 和浓硫酸 (10 mL), 冰水浴降温到 0-5 °C。分批缓慢加入硝酸钾 (542 mg, 1.1 eq), 保温反应 1-2 h。将反应液缓慢滴加入纯化水 (200 mL), 用碳酸钠固体调节 pH 到中性, 用乙酸乙酯 (50 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压
10 浓缩得 750 mg 产品。

第三步: 4-环丙氧基-2-氟-5-硝基苯胺



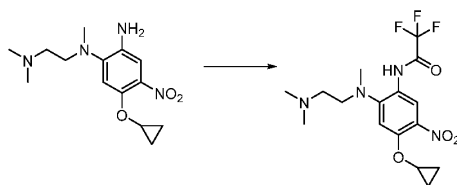
向 100 mL 三口瓶中加入 2, 4-二氟-5-硝基苯胺 (650 mg) 和 DMF (20 mL), 冰水
浴降温到 0-5 °C, 加入环丙醇 (216.8 mg, 1 eq)。然后分批缓慢加入叔丁醇钠 (466 mg,
15 1.3 eq) 保温反应 1-2 h。将反应液倒入纯化水 (100 mL), 用乙酸乙酯 (50 mL × 3) 萃取
3 次, 合并有机相, 饱和食盐水洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩
得粗品, 粗品经柱层析纯化, 洗脱液: PE/EA = 10/1, 收集产品, 减压浓缩得 392 mg 产
品。

第四步：5-环丙氧基 N1-(2-(二甲基氨基)乙基)-N1-甲基-4-硝基苯-1,2-二胺



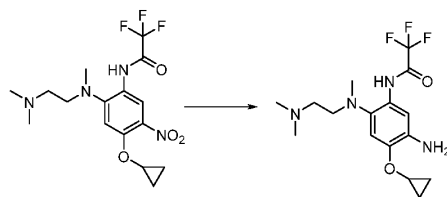
于 100 mL 三口瓶中依次加入 4-环丙氧基-2-氟-5-硝基苯胺 (300 mg), DMF (5 mL), N1, N1, N2-三甲基乙二胺 (433 mg, 3 eq) 和 DIPEA (548 mg, 3 eq), 磁力搅拌溶解, 5 油浴升温至 50-60 °C, 搅拌反应 6-7 h。反应结束后, 自然降温到室温, 加入纯化水 (50 mL), 用乙酸乙酯 (30 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 20/1, 收集产品, 减压浓缩得 292 mg 产品。

第五步：N-(4-环丙氧基-2-((2-(二甲基氨基)乙基)(甲基)氨基)-5-硝基苯基)-2,2,2-三氟乙酰胺



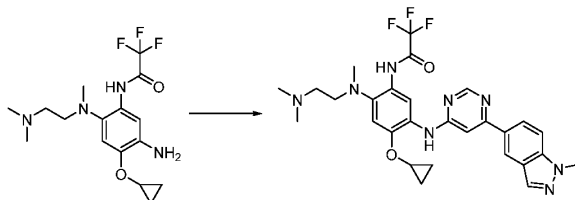
向 100 mL 三口瓶中加入 5-环丙氧基 N1-(2-(二甲基氨基)乙基)-N1-甲基-4-硝基苯-1,2-二胺 (310 mg) 和乙酸乙酯 (25 mL), 室温搅拌下滴加三氟乙酸酐 (243 mg, 1.1 eq) 的乙酸乙酯 (0.5 mL) 溶液, 滴加完毕后, 室温搅拌反应 1 h。加入纯化水 (50 mL), 15 用乙酸乙酯 (30 mL × 3) 萃取 3 次, 合并有机相, 饱和食盐水洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得 300 mg 产品。

第六步：N-(5-氨基-4-环丙基-2-((2-(二甲基氨基)乙基)(甲基)氨基)苯基)-2,2,2-三氟乙酰胺



于 100 mL 单口瓶中依次加入 N-(4-环丙氧基-2-((2-(二甲基氨基)乙基)(甲基)氨基)-5-硝基苯基)-2,2,2-三氟乙酰胺 (300 mg), 甲醇 (10 mL) 和 Pd/C (30 mg), 置换氢气三次, 室温反应 2-3 h。过滤, 滤液减压浓缩得 300 mg 油状产品。

- 5 第七步: N-(4-环丙氧基-2-((2-(二甲基氨基)乙基)(甲基)氨基)-5-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)苯基)-2,2,2-三氟乙酰胺

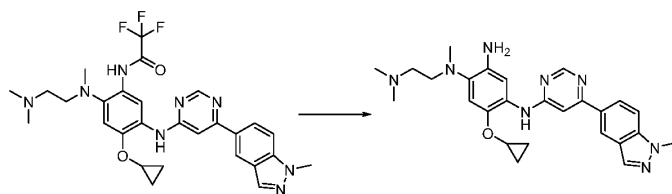


氮气保护下, 于 100 mL 三口瓶中依次加入 N-(5-氨基-4-环丙基-2-((2-(二甲基氨基)乙基)(甲基)氨基)苯基)-2,2,2-三氟乙酰胺 (80 mg), 中间体 A1 (54 mg, 1 eq),

- 10 碳酸铯 (144 mg, 2 eq), Xantphos (26 mg, 0.2 eq), 甲苯 (10 mL) 和 $\text{Pd}_2(\text{dba})_3$ (20 mg, 0.1 eq), 油浴升温到 90-95 °C, 搅拌反应 8-10 h。降温至室温, 反应液减压浓缩得粗产品, 粗产品经柱层析纯化, 洗脱液: DCM/MeOH = 10/1, 收集产品, 减压浓缩得 80 mg 产品。

- 第八步: 5-环丙氧基 N1-(2-(二甲基氨基)乙基)-N1-甲基-N4-(6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)苯-1,2,4-三胺

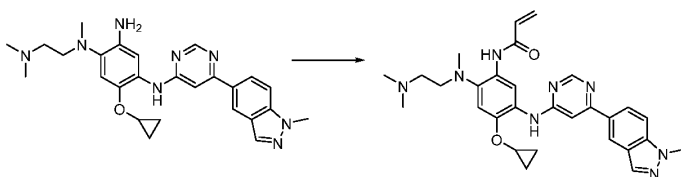
- 15



于 100 mL 单口瓶中加入 N-(4-环丙氧基-2-((2-(二甲基氨基)乙基)(甲基)氨基)-5-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)苯基)-2,2,2-三氟乙酰胺 (80 mg) 和乙醇/水 = 1/1 的 1N 哌啶溶液 (8 mL), 室温搅拌反应 8-10 h。加入纯化水 (30 mL),

5 乙酸乙酯 (30 mL), 分液, 水相用乙酸乙酯萃取 2 次, 合并有机相, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 10/1, 收集产品, 减压浓缩得 50 mg 产物。

第九步: N-(4-环丙氧基-2-((2-(二甲基氨基)乙基)(甲基)氨基)-5-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)苯基)丙烯酰胺



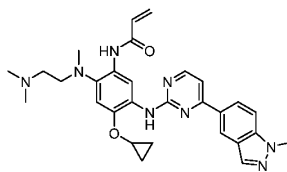
10

以 5-环丙氧基-N1-(2-(二甲基氨基)乙基)-N1-甲基-N4-(6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)苯-1,2,4-三胺为原料,按照实施例 167 第三步合成方法制备终产物 291。

MS (ESI⁺) m/z = 527.06 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.25 (s, 1H), 9.19 (s, 1H), 8.61 (s, 1H), 8.53 (s, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 8.12 (dd, *J* = 8.9, 1.0 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.30 (s, 1H), 7.18 (s, 1H), 6.62-6.68 (m, 1H), 6.23 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.71 (dd, *J* = 12.0, 1.5 Hz, 1H), 4.08 (s, 3H), 3.93-3.96 (m, 1H), 2.98 (s, 2H), 2.71 (s, 3H), 2.36-2.49 (m, 2H), 2.20 (brs, 6H), 0.76-0.82 (m, 4H).

实施例 441. 终产物 292 制备

N- (4-环丙氧基-2- ((2- (二甲基氨基) 乙基) (甲基) 氨基) -5- ((4- (1-甲基-1H-吡唑-5-基) 嘧啶-2-基) 氨基) 苯基) 丙烯酰胺 (终产物 292)

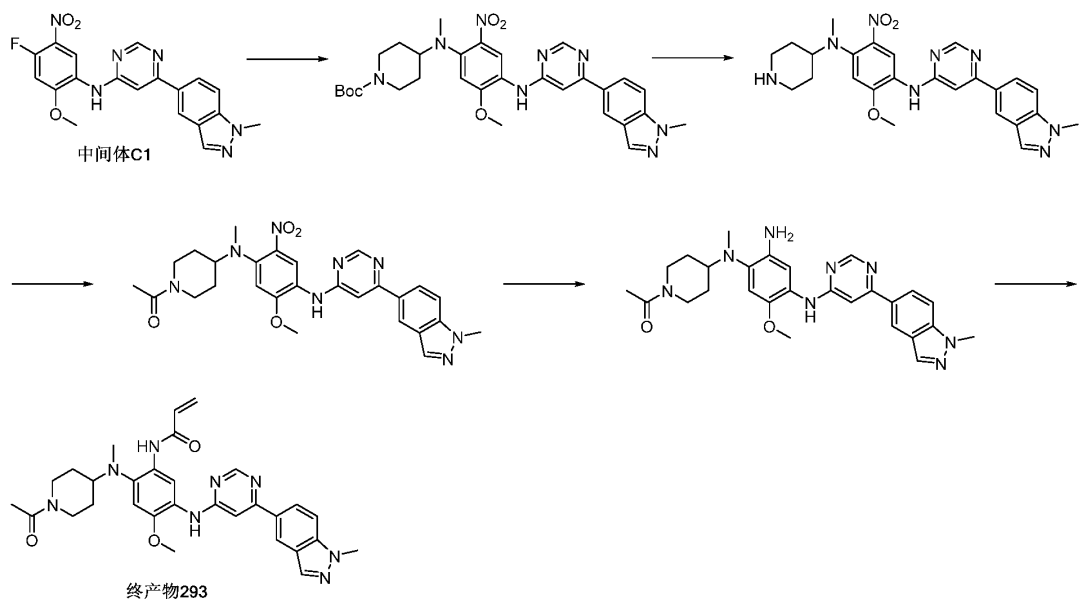


以 2, 4-二氟苯胺和中间体 A3 为原料, 按照合成终产物 291 的方法制备终产物 292。

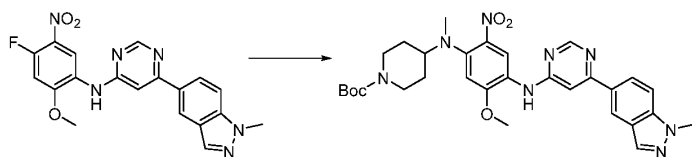
- 5 MS (ESI⁺) m/z = 527.26 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15-9.19 (m, 3H), 8.85 (s, 1H), 8.48 (d, *J* = 5.0 Hz, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 8.12 (s, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.44 (d, *J* = 5.0 Hz, 1H), 7.26 (s, 1H), 6.68-6.75 (m, 1H), 6.32 (d, *J* = 17.1 Hz, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 4.09 (s, 3H), 3.93 (brs, 1H), 2.93 (t, *J* = 6.0 Hz, 2H), 2.71 (s, 3H), 2.35 (t, *J* = 5.6 Hz, 2H), 2.18 (s, 6H), 0.76-0.80 (m, 4H).

10 实施例 442. 终产物 293 制备

N- (2- ((1-乙酰基哌啶-4-基) (甲基) 氨基) -4-甲氧基-5- ((6- (1-甲基-1H-吡唑-5-基) 嘧啶-4-基) 氨基) 苯基) 丙烯酰胺 (终产物 293)



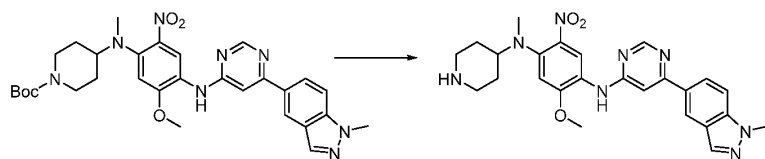
第一步: ((5-甲氧基-4-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)-2-硝基苯基)(甲基)氨基)哌啶-1-甲酸叔丁酯



5

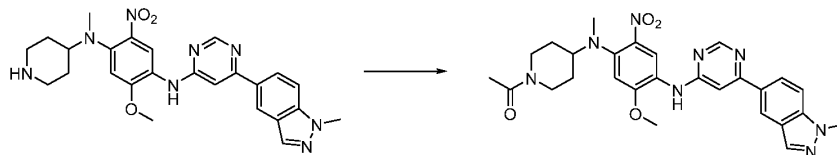
于 100 mL 三口瓶中加入中间体 C1 (300 mg, 0.76 mmol), 碳酸钾 (726 mg, 9 eq), 1-叔丁氧羰基-4-甲氨基哌啶 (489 mg, 3 eq), 碘化钾 (758 mg, 6 eq) 和 DMF (20 mL), 油浴升温到 50-60 °C, 搅拌反应 3 天, 降温至室温, 加入纯化水 (20 mL), DCM (20 mL), 分液, 水相用 DCM (30 mL × 4) 萃取 4 次, 合并有机相, 饱和食盐水 (30 mL × 3) 洗 3 10 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱液: DCM/MeOH = 50/1, 收集产品, 减压浓缩得 340 mg 红色固体。

第二步: 2-甲氧基-N4-甲基-N1-(6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)-5-硝基-N4-(哌啶-4-基)苯-1, 4-二胺



于 100 mL 单口瓶中加入 (5-甲氧基-4-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)-2-硝基苯基)(甲基)氨基)哌啶-1-甲酸叔丁酯 (340 mg, 0.6 mmol) 和 DCM (5 mL), 搅拌溶解后, 向体系中滴加三氟乙酸 (4 mL), 滴毕室温搅拌反应。TLC 监控反应, 反应结束后, 将体系浓缩, 用饱和碳酸氢钠溶液调 pH = 9, DCM (30 mL × 3) 萃取 3 次, 合并有机相, 无水硫酸钠干燥 30 min, 抽滤, 滤液减压浓缩得粗品, 粗品经柱层析纯化, 洗脱剂: DCM/MeOH = 10/1, 收集产品, 减压浓缩得 120 mg 产品。

第三步: 1-(4-((5-甲氧基-4-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)-2-硝基苯基)(甲基)氨基)哌啶-1-基)乙酮

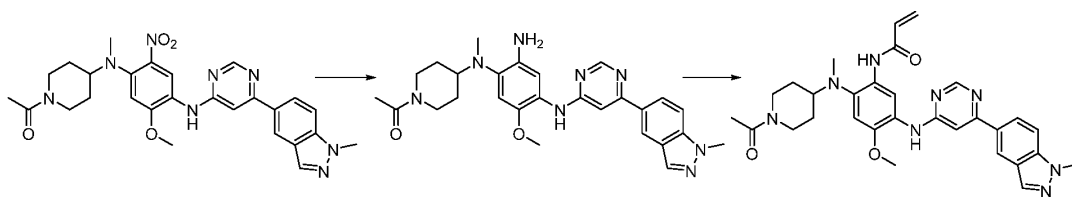


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于 100 mL 三口瓶中加入 2-甲氧基-N4-甲基-N1-(6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)-5-硝基-N4-(哌啶-4-基)苯-1,4-二胺 (120 mg, 0.25 mmol), 三乙胺 (50 mg, 2 eq) 和 DCM (15 mL), 搅拌溶解。降温至 0-5 °C, 向体系中滴加醋酸酐 (30 mg, 1.2 eq), 滴毕升至室温搅拌。TLC 监控反应进程, 反应结束后, 加入纯化水 (20 mL), 乙酸乙酯 (30 mL), 分液, 水相用乙酸乙酯 (30 mL × 3) 萃取 3 次, 合并有机相, 用饱和食盐水 (30 mL × 2) 洗 2 次, 无水硫酸钠干燥 30 min, 过滤, 滤液减压浓缩得 100 mg 粗品。

15

第四、五步: N-(2-((1-乙酰基哌啶-4-基)(甲基)氨基)-4-甲氧基-5-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)苯基)丙烯酰胺

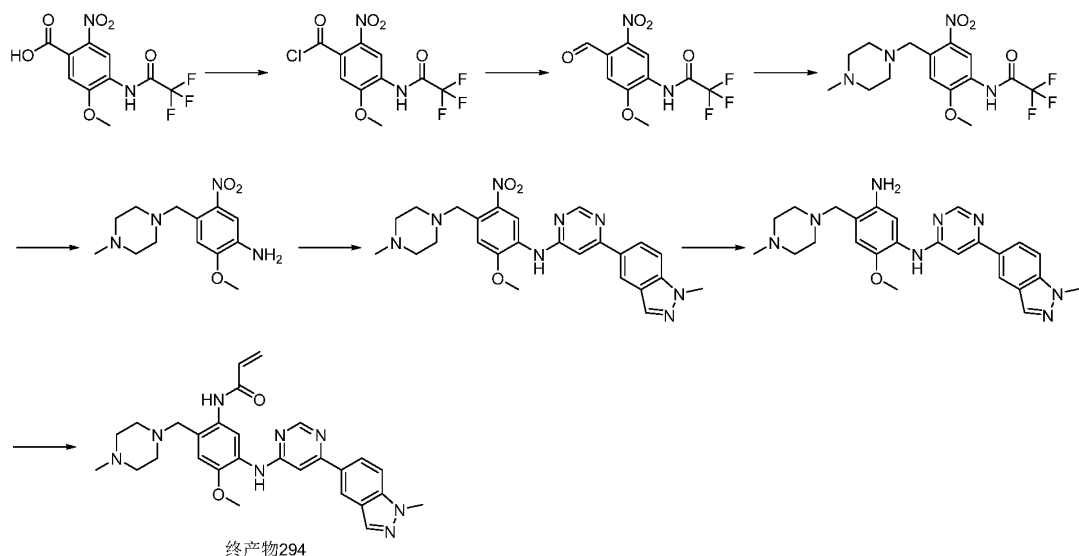


以 1-(4-((5-甲氧基-4-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)-2-硝基苯基)(甲基)氨基)哌啶-1-基)乙酮为原料, 按照实施例 167 第二、三步合成方法制备终产物 **293**。

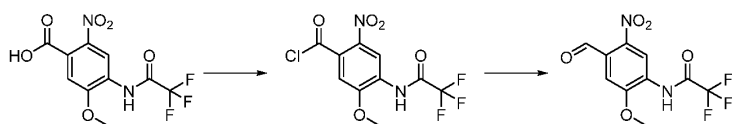
- 5 MS (ESI⁺) $m/z = 555.30$ [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.14 (s, 1H), 8.75 (s, 1H), 8.61 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.09 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.77 (d, $J = 9.2$ Hz, 1H), 7.43 (s, 1H), 6.95 (s, 1H), 6.61-6.68 (m, 1H), 6.26 (dd, $J = 16.8, 1.2$ Hz, 1H), 5.74 (d, $J = 11.6$ Hz, 1H), 4.38 (d, $J = 12.8$ Hz, 1H), 4.09 (s, 3H), 3.85 (s, 3H), 3.79-3.84 (m, 1H), 2.92-2.97 (m, 2H), 2.63 (s, 2H), 2.44-2.48 (m, 2H), 1.98 (s, 3H), 1.74-1.78 (m, 2H), 1.37-1.50 (m, 2H).

实施例 443. 终产物 **294** 制备

N-(2-(4-甲基哌嗪-1-基)甲基)-4-甲氧基-5-[[6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基]氨基]苯基) 丙烯酰胺 (终产物 **294**)



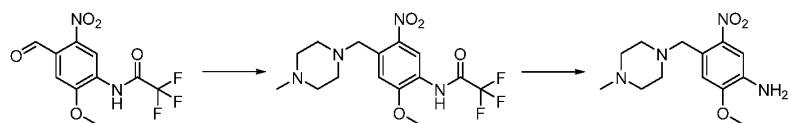
第一步：2,2,2-三氟-N-(4-甲酰基-2-甲氧基-5-硝基苯基)乙酰胺



氩气保护下,于 100 mL 三口瓶中依次加入 5-甲氧基-2-硝基-4-(2,2,2-三氟乙酰氨基)

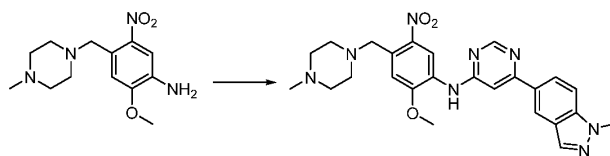
- 5 苯甲酸(1g, 3.24 mmol), DCM (10 mL) 和 2 滴 DMF, 室温搅拌下滴加草酰氯 (824 mg, 2 eq) 的 DCM 溶液 (1 mL), 保温搅拌 1 h 至体系全部澄清。将反应液转入 100 mL 单口瓶, 减压浓缩至剩余三分之一, 加入甲苯 20 mL, 室温减压浓缩。氩气保护下, 将剩余物转入 100 mL 三口瓶, 降温至 0-5 °C, 加入四三苯基磷 (374 mg), 然后缓慢滴加三丁基氢化锡 (1400 mg), 约 30 min, 滴毕, 保温搅拌反应 2 h, 再升温到室温反应过夜。反应完毕后, 将反应液减压浓缩, 经柱层析纯化, 用 PE/EA = 5/1 洗脱, 收集产品并减压浓缩得 446 mg, 收率: 47%。

第二步：2-甲氧基-4-((4-甲基哌嗪-1-基)甲基)-5-硝基苯胺



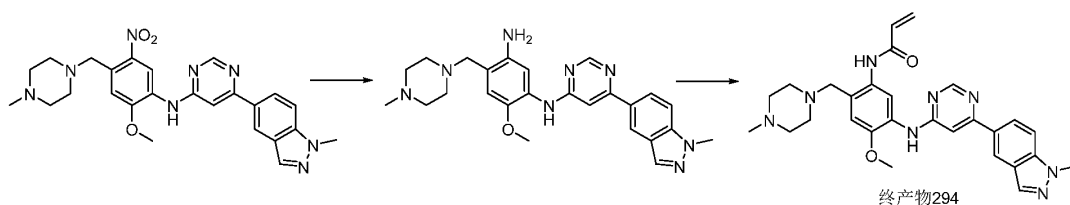
于 100 mL 三口瓶中依次加入 2,2,2-三氟-N-(4-甲酰基-2-甲氧基-5-硝基苯基) 乙酰胺 (100 mg, 0.34 mmol), 甲醇 (5 mL), 1-2 滴醋酸, N-甲基哌嗪 (34 mg, 0.34 mmol), 室温搅拌下分批加入氰基硼氢化钠 (64 mg, 1.0 mmol) 约 10 min, 加毕, 室温搅拌反应约 6-7 h。反应完毕后, 加入 1 N 氢氧化钠水溶液 (5 mL) 室温搅拌, TLC 监控反应, 反应完毕后, 加入 20 mL 纯化水, 20 mL 乙酸乙酯, 搅拌 5 min, 分液, 水相用乙酸乙酯 (20 mL × 2) 萃取 2 次, 合并有机相, 用饱和食盐水洗 2 次, 无水硫酸钠干燥 30 min, 减压浓缩得粗品, 粗品经柱层析纯化, 用 DCM/MeOH = 50/1 → 10/1 梯度洗脱, 收集产品并减压浓缩得 30 mg。

第三步: N-(2-甲氧基-4-((4-甲基哌嗪-1-基) 甲基)-5-硝基苯基)-6-(1-甲基-1H-吡唑-5-基) 嘧啶-4-胺



以 2-甲氧基-4-((4-甲基哌嗪-1-基) 甲基)-5-硝基苯胺和中间体 A1 为原料, 制备过程参见实施例 150。

第四、五步: N-(2-(4-甲基哌嗪-1-基) 甲基)-4-甲氧基-5-[[6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基]氨基]苯基) 丙烯酰胺



以 N-(2-甲氧基-4-((4-甲基哌嗪-1-基) 甲基)-5-硝基苯基)-6-(1-甲基-1H-吡唑-5-

基) 嘧啶-4-胺为原料, 制备过程参见实施例 167 第二、三步。

MS (ESI⁺) $m/z = 513.16$ [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.62 (s, 1H), 8.81 (s, 1H),

8.66 (s, 1H), 8.63 (d, $J = 0.5$ Hz, 1H), 8.50 (d, $J = 0.5$ Hz, 1H), 8.17 (d, $J = 0.5$ Hz, 1H), 8.08

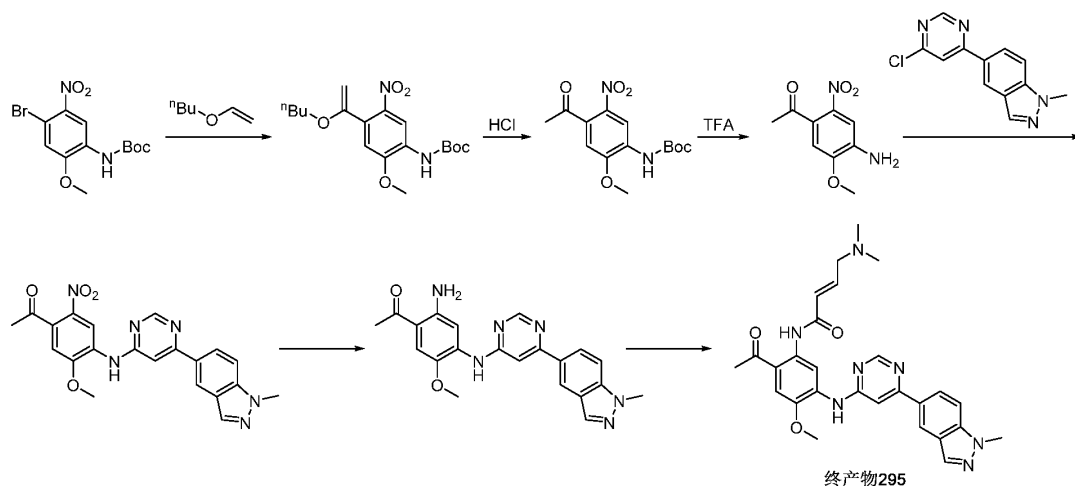
(dd, $J = 1.5, 9.0$ Hz, 1H), 7.76 (d, $J = 9.0$ Hz, 1H), 7.48 (s, 1H), 7.01 (s, 1H), 6.30-6.36 (m, 1H),

5 6.23 (dd, $J = 2.0, 17.0$ Hz, 1H), 5.79 (dd, $J = 1.5, 10.0$ Hz, 1H), 4.09 (s, 3H), 3.84 (s, 3H), 3.59 (s,

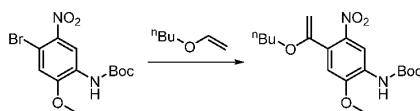
2H), 2.30-2.50 (m, 8H), 2.19 (s, 3H).

实施例 444. 终产物 295 制备

(E)-4-(二甲基氨基)-N-(2-乙酰基-4-甲氧基-5-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)苯基)丁-2-烯酰胺 (终产物 295)



第一步: (4-(1-丁氧基乙烯基)-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯



氩气保护下, 向 100 mL 单口瓶中依次加入 (4-溴-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯

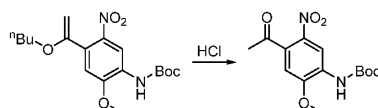
叔丁酯 (1.4g, 4.04 mmol), 1-(乙烯氧基)丁烷 (4.04g, 40.4 mmol), 三乙胺 (531.2 mg,

15 5.26 mmol), 正丁醇 (60 mL) 和 Pd(PPh₃)₄ (468 mg, 0.404 mmol)。升温至 110 °C 反应

12 h。降温至室温，向反应液中加入 50 mL 水，用乙酸乙酯（50 mL × 3）萃取 3 次，合并有机相，浓缩，得到粗品。粗品经柱层析纯化，用 PE/EA = 100/1 洗脱，收集产品并减压浓缩，得到 1.4 g 淡黄色油状物，收率：94.6%。

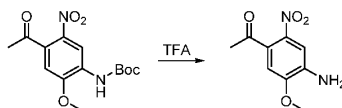
第二步：(4-乙酰基-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯

5



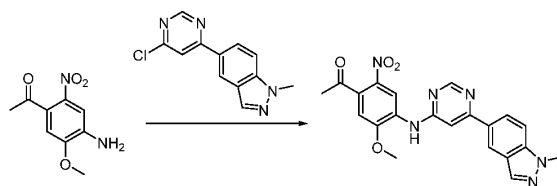
向 100 mL 单口瓶中依次加入 (4-(1-丁氧基乙烯基)-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯 (1.4 g, 3.8 mmol)，四氢呋喃 (30 mL) 和 3 N HCl (12 mL)，加毕，室温搅拌反应 1 h。原料反应完全，加入 50 mL 饱和碳酸钠水溶液调 pH>7，用乙酸乙酯 (50 mL × 3) 萃取 3 次，合并有机相，浓缩，得到 1.0 g 淡黄色油状物，收率：84.7%。

10 第三步：1-(4-氨基-5-甲氧基-2-硝基苯基)乙-1-酮



向 100 mL 单口瓶中依次加入 (4-乙酰基-2-甲氧基-5-硝基苯基)氨基甲酸叔丁酯 (1.0 g, 3.22 mmol)，二氯甲烷 (20 mL) 和三氟乙酸 (8 mL)。加毕，室温反应 1 h，加入 60 mL 饱和碳酸钠水溶液调 pH>7，水相用二氯甲烷 (50 mL × 2) 萃取 2 次，合并有机相，
15 浓缩，得到 520 mg 淡黄色固体，收率：76.8%。

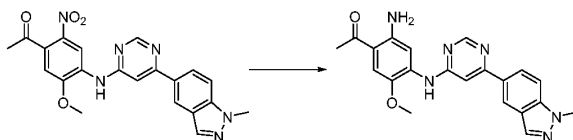
第四步：1-(5-甲氧基-4-((6-(1-甲基-1H-吡唑-5-基)嘧啶-4-基)氨基)-2-硝基苯基)乙-1-酮



以 1-(4-氨基-5-甲氧基-2-硝基苯基)乙-1-酮 (162 mg, 0.771 mmol) 和中间体 A1 为原料, DME 为溶剂, 制备过程参见实施例 150。

第五步: 1-(2-氨基-5-甲氧基-4-((6-(1-甲基-1H-咪唑-5-基)嘧啶-4-基)氨基)苯基)

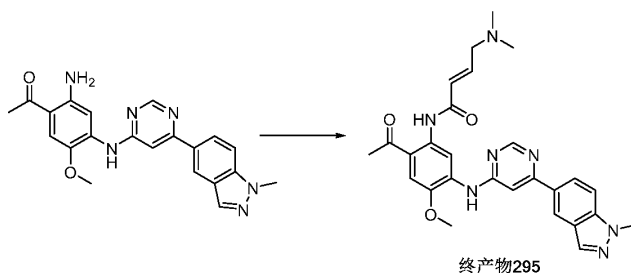
5 乙-1-酮



向 100 mL 单口瓶中依次加入 1-(5-甲氧基-4-((6-(1-甲基-1H-咪唑-5-基)嘧啶-4-基)氨基)-2-硝基苯基)乙-1-酮 (100 mg, 0.24 mmol), 四氢呋喃/二氯甲烷 = 1/1 (20 mL) 和 Pd/C (10 mg)。加毕, 室温加氢反应 10 h。过滤, 滤液减压浓缩, 得到 70 mg 淡黄色

10 固体, 收率: 75.4%。

第六步: (E)-4-(二甲基氨基)-N-(2-乙酰基-4-甲氧基-5-((6-(1-甲基-1H-咪唑-5-基)嘧啶-4-基)氨基)苯基)丁-2-烯酰胺



向 50 mL 单口瓶中依次加入反式-4-二甲基氨基巴豆酸盐 (220 mg, 1.70 mmol), 乙腈 (3 mL) 和 1 滴 DMF, 室温下滴加草酰氯 (600 mg, 4.76 mmol), 加毕, 升温至 45 °C 反应 0.5-1 h, 原料反应完全, 减压浓缩, 得到 200 mg 黑色油状物。

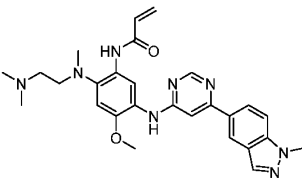
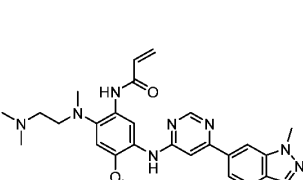
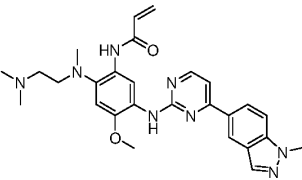
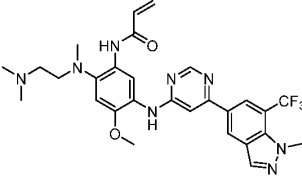
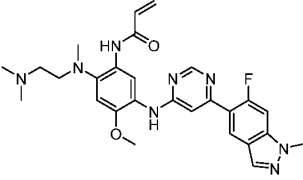
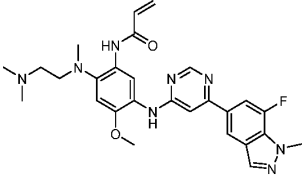
向 100 mL 单口瓶中依次加入 1- (2-氨基-5-甲氧基-4- ((6- (1-甲基-1H-吡唑-5-基) 嘧啶-4-基)氨基)苯基)乙-1-酮(70 mg, 0.18 mmol)和二氯甲烷(10 mL), 降温至 0-5 °C, 滴加 (E) -4- (二甲基氨基) 丁-2-烯酰氯 (80.7 mg, 0.549 mmol) 的乙腈溶液 (2 mL)。加毕, 室温反应 30 min, 向反应液中加入 30 mL 饱和碳酸氢钠水溶液, 水相用二氯甲烷 (50 mL × 3) 萃取 3 次, 合并有机相, 减压浓缩得到粗品。粗品经薄层制备板纯化, 得 6 mg 淡黄色固体, 收率: 7%。

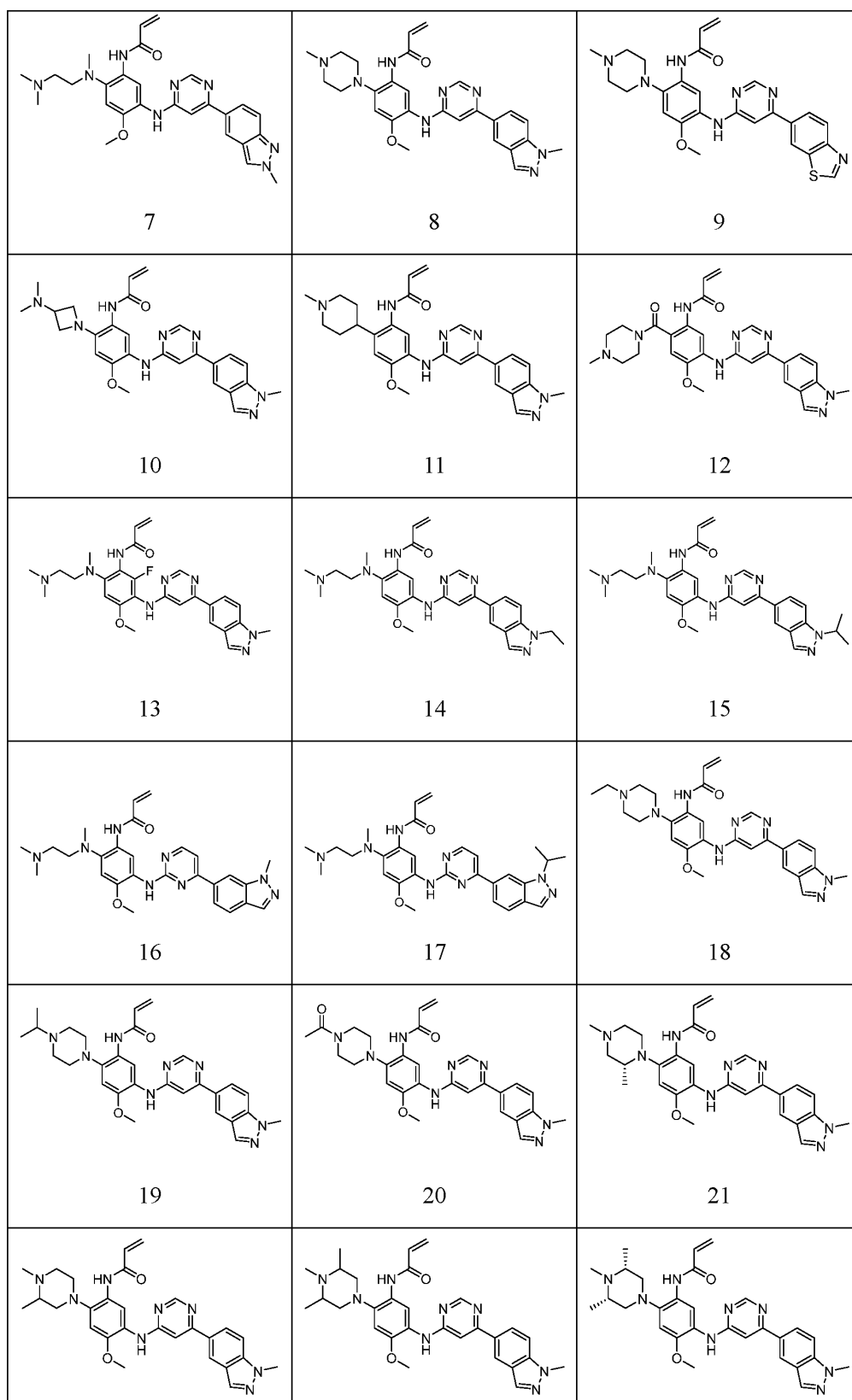
MS (ESI⁺) m/z = 500.12 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.54 (s, 1H), 9.51 (s, 1H), 9.12 (s, 1H), 8.79 (s, 1H), 8.55 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.52 (s, 1H), 6.74-6.80 (m, 1H), 6.21 (d, *J* = 15.5 Hz, 1H), 4.10 (s, 3H), 3.99 (s, 3H), 3.10 (d, *J* = 11.0 Hz, 2H), 2.64 (s, 3H), 2.20 (s, 6H).

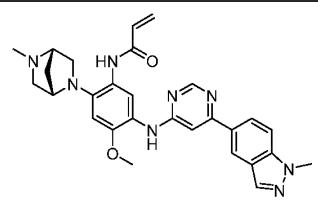
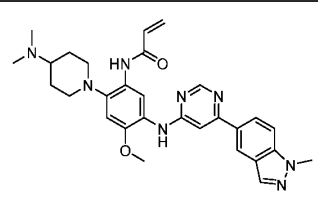
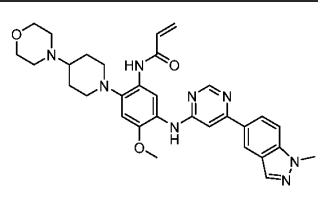
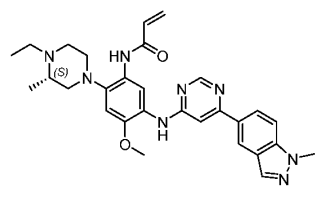
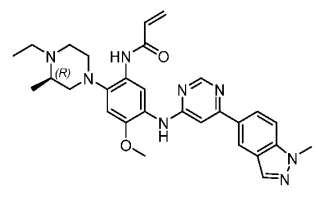
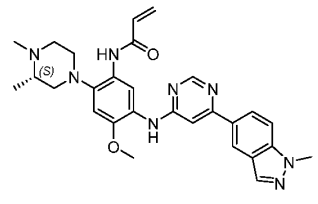
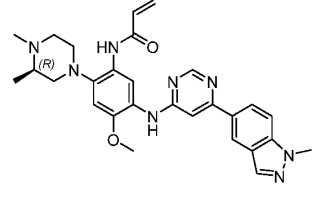
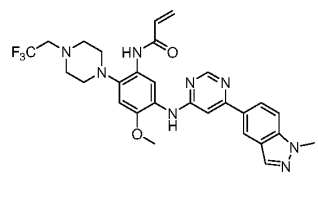
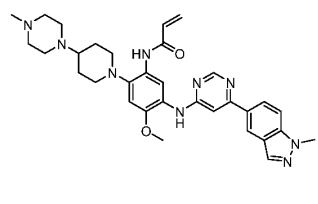
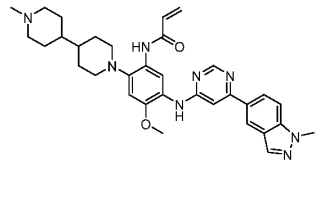
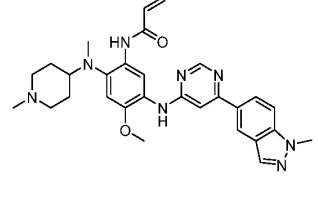
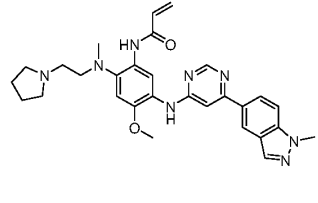
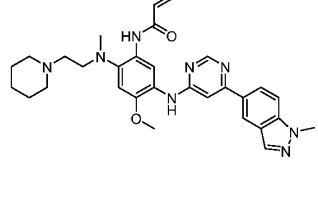
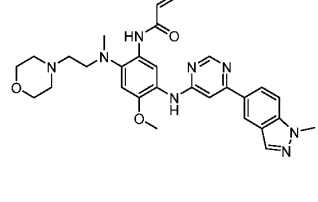
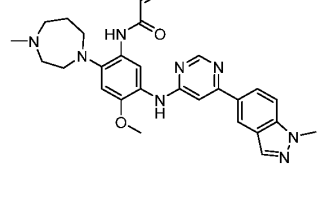
实施例 445. 终产物 296 的制备

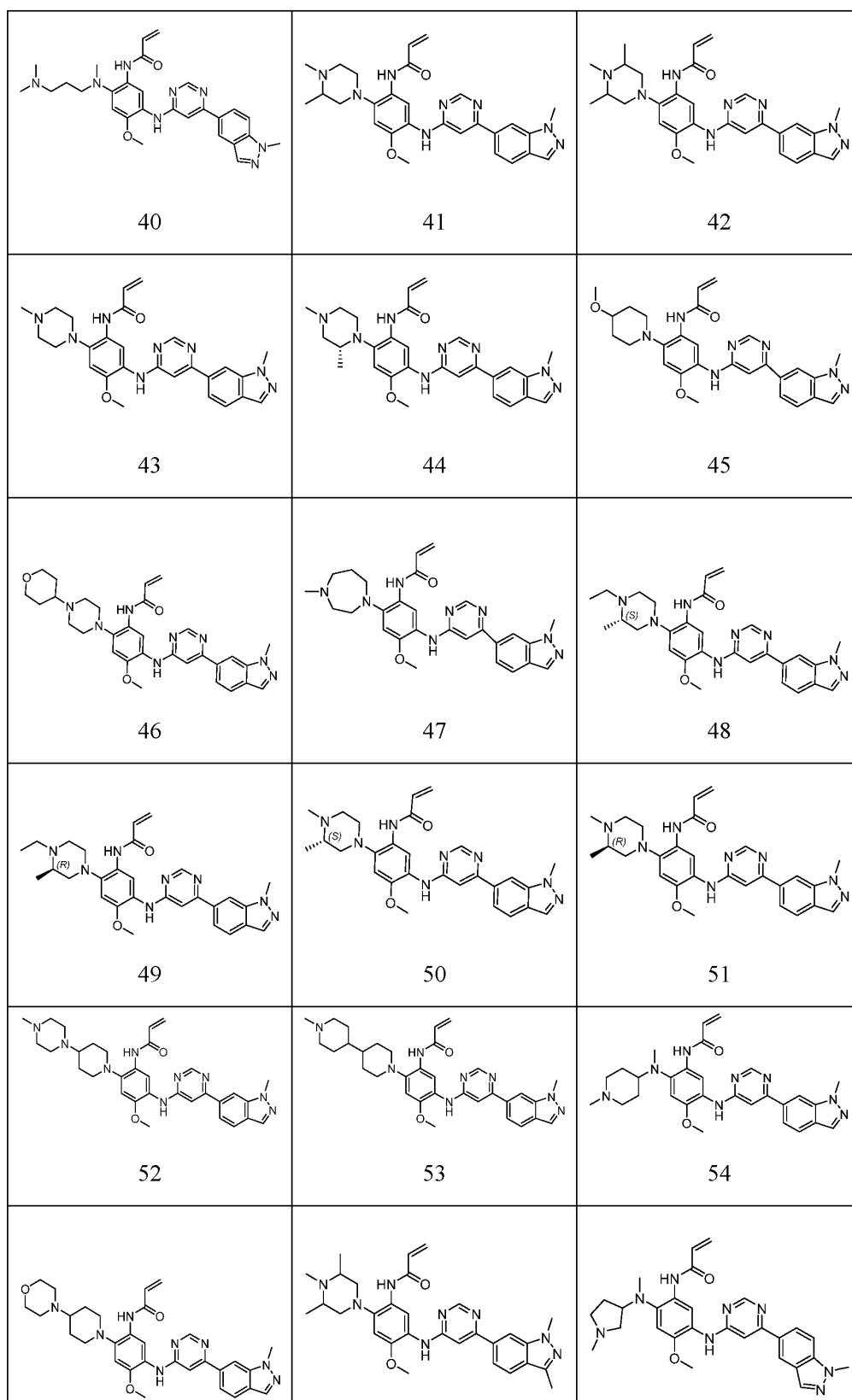
应用 CN102083800A 中实施例 92 的方法合成该专利中已知化合物(终产物 296)(见表 7)。

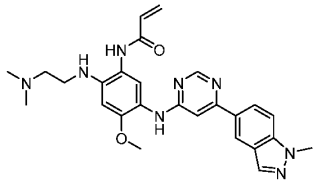
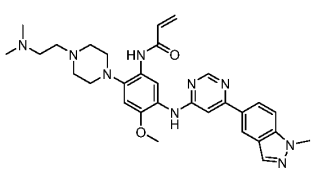
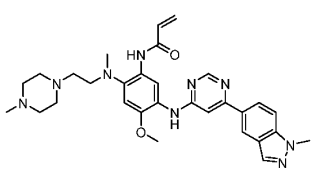
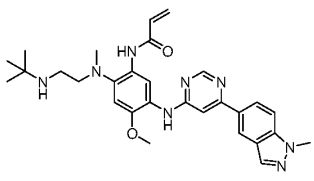
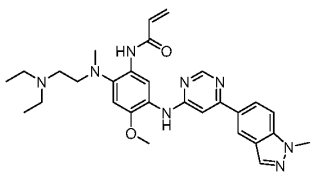
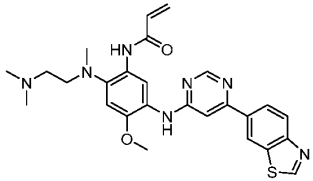
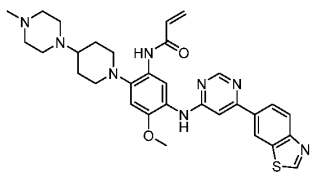
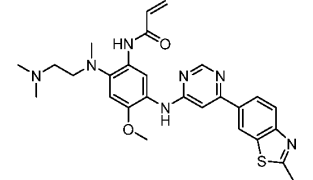
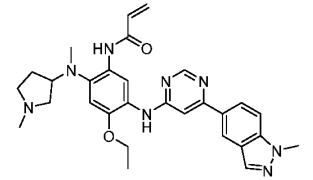
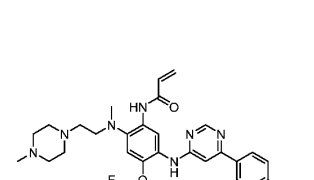
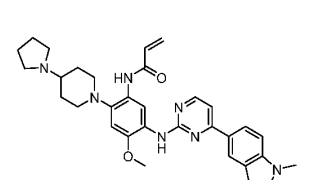
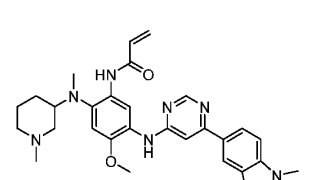
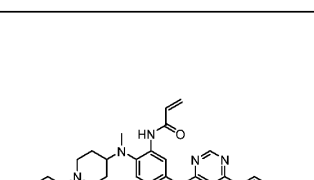
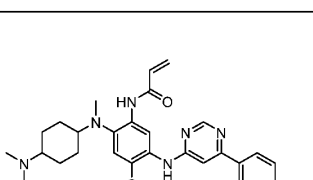
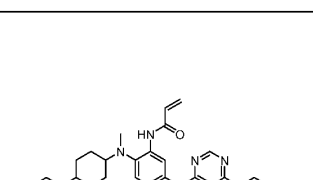
表 7. 作为 EGFR 激酶抑制剂的化合物 (终产物)

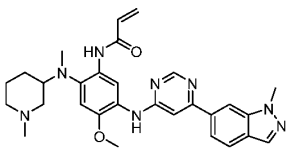
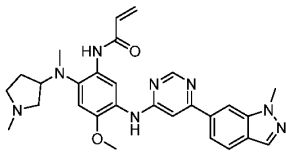
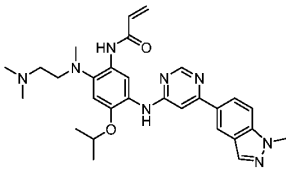
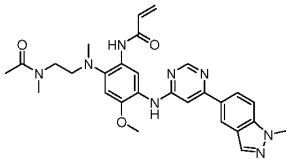
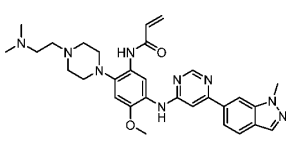
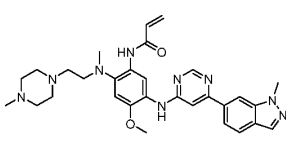
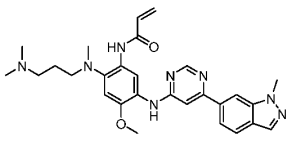
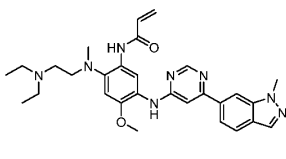
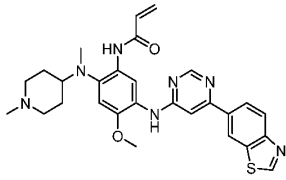
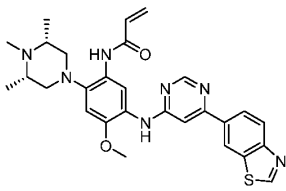
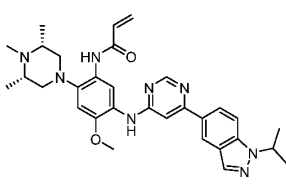
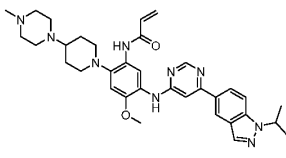
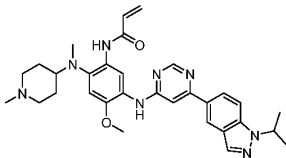
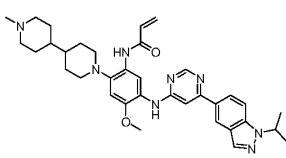
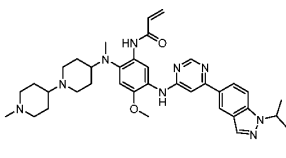
 1	 2	 3
 4	 5	 6

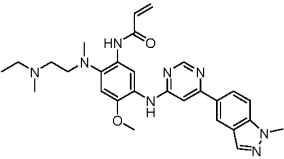
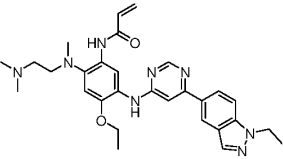
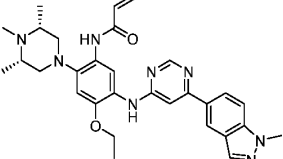
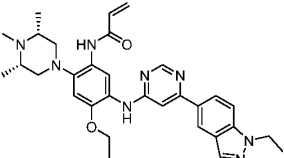
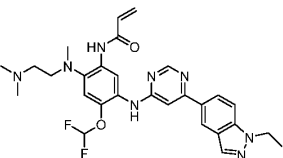
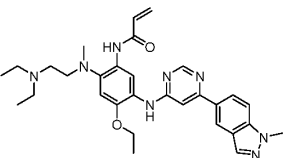
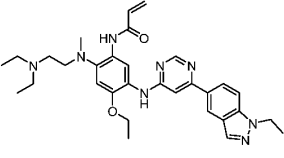
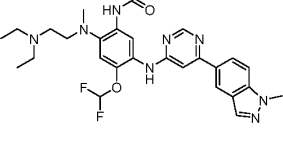
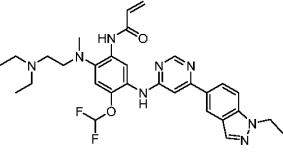
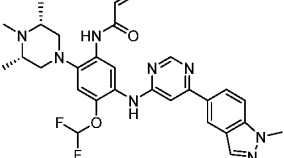
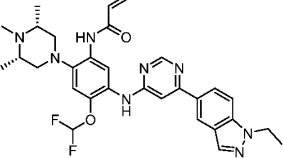
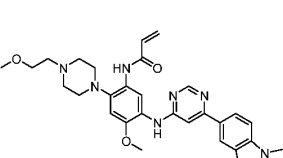
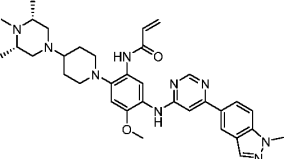
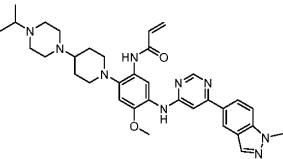
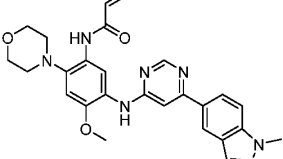


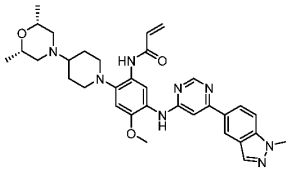
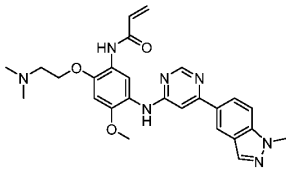
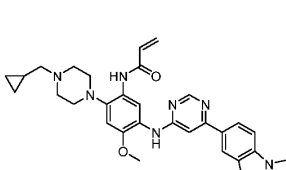
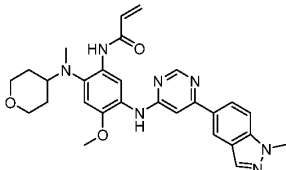
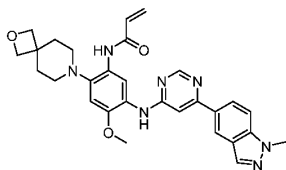
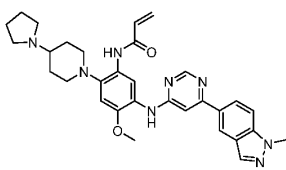
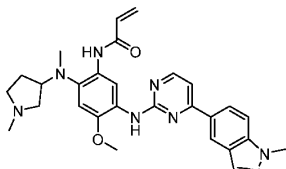
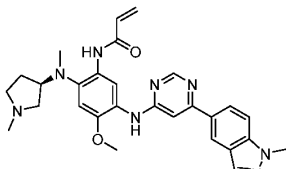
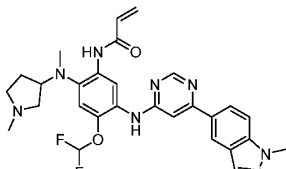
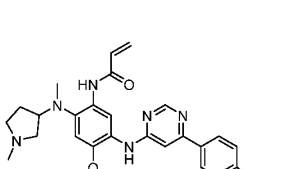
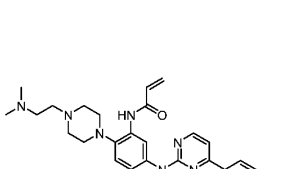
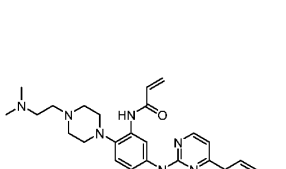
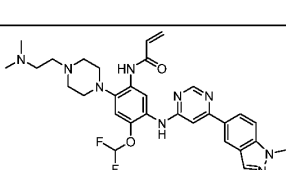
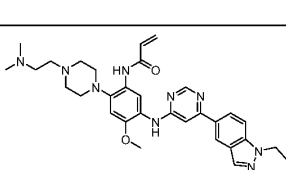
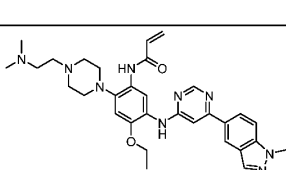
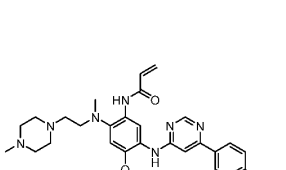
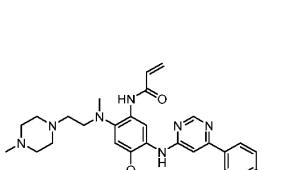
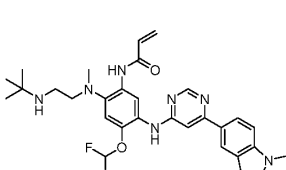
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 37	 38	 39

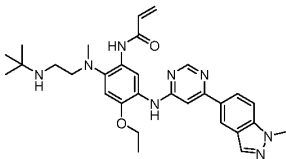
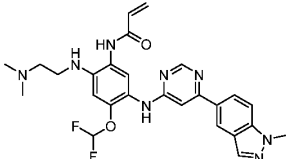
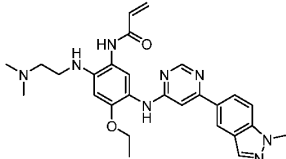
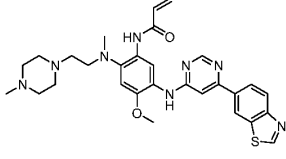
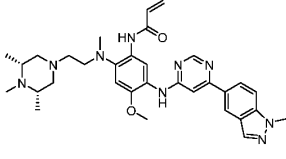
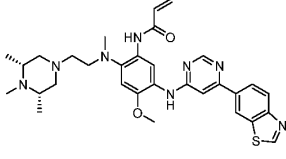
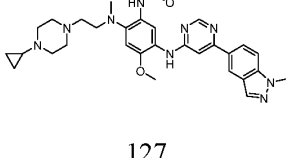
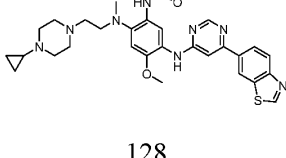
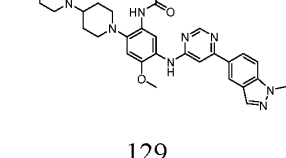
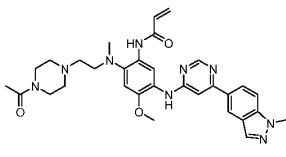
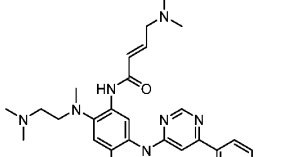
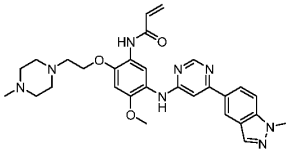
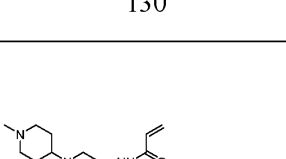
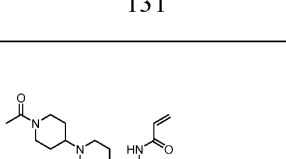
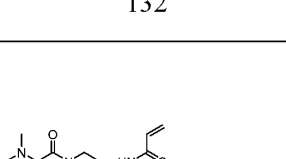


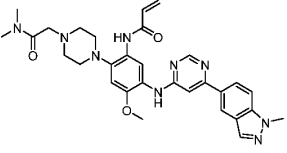
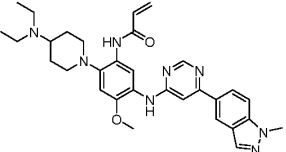
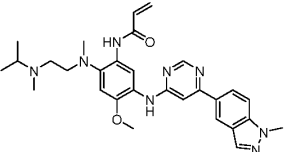
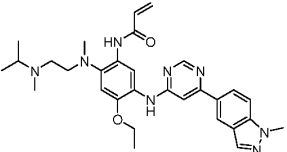
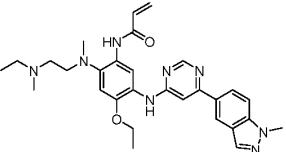
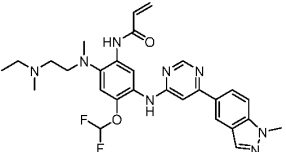
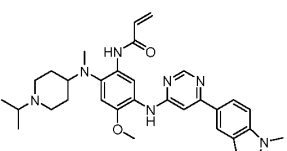
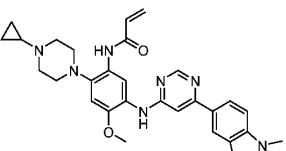
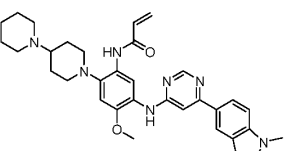
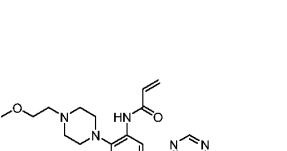
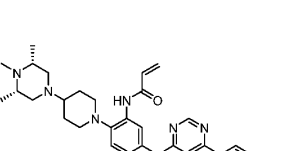
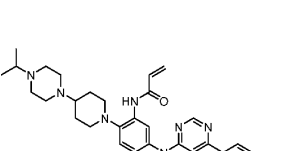
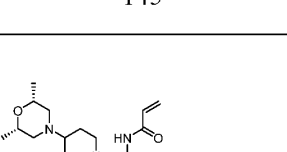
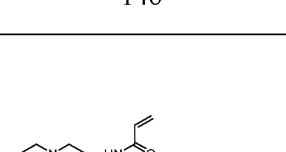
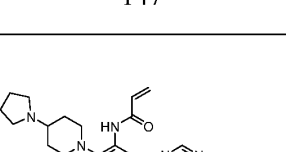
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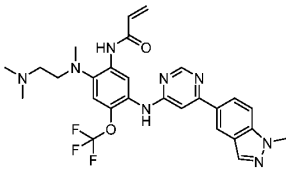
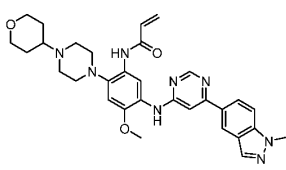
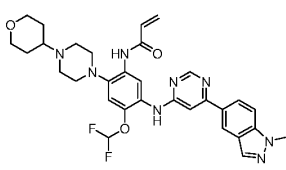
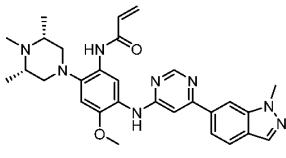
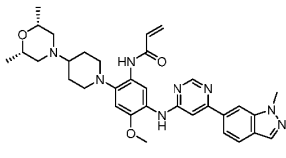
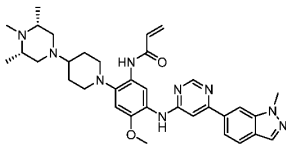
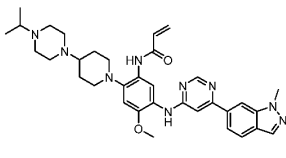
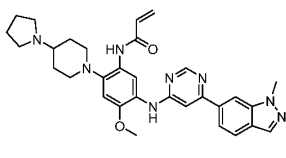
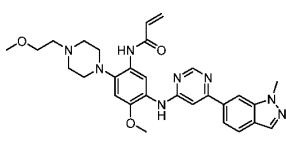
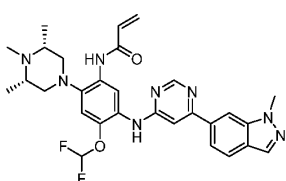
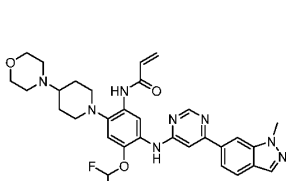
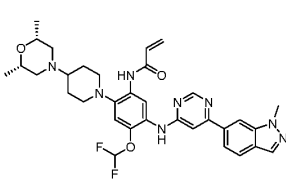
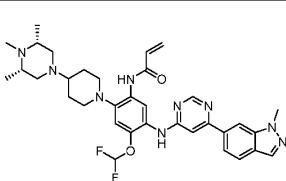
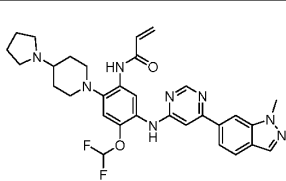
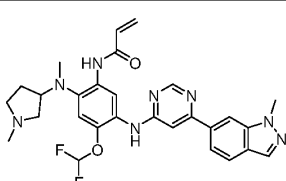
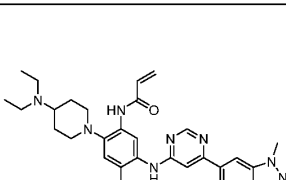
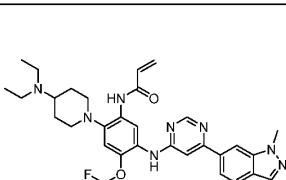
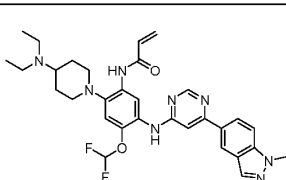
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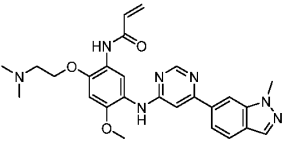
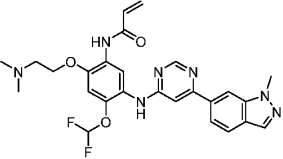
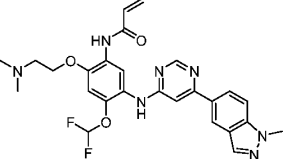
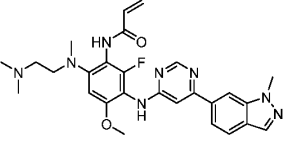
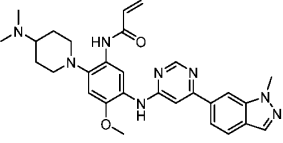
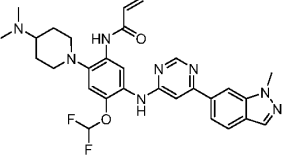
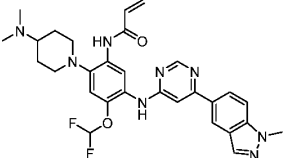
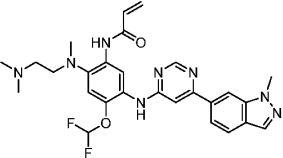
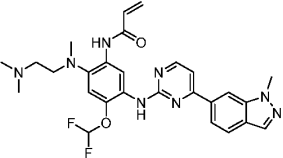
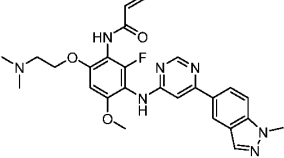
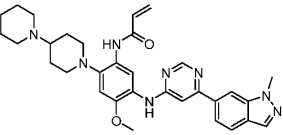
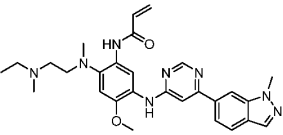
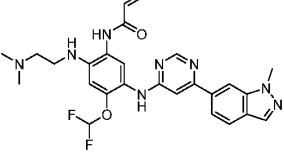
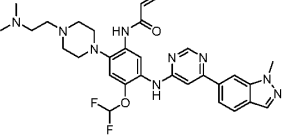
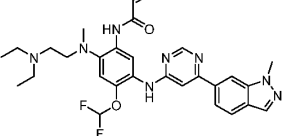
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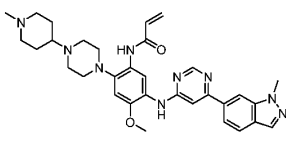
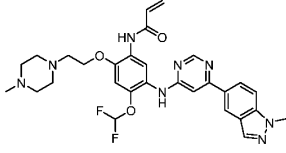
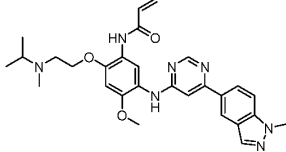
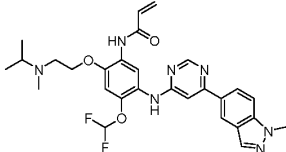
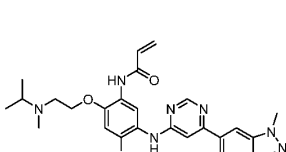
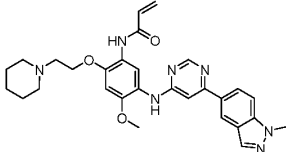
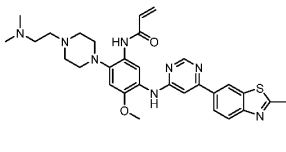
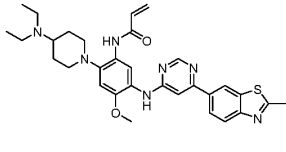
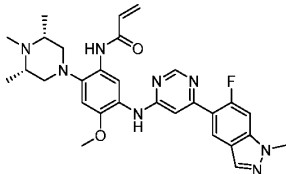
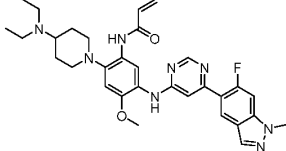
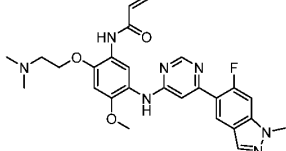
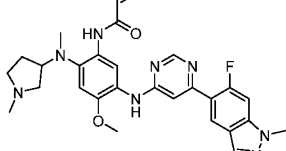
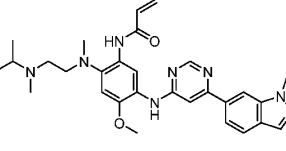
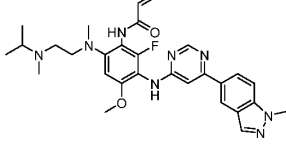
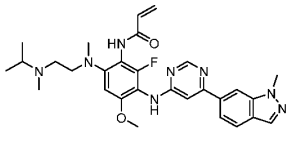
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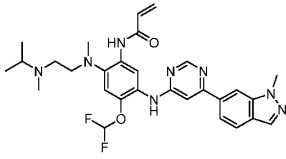
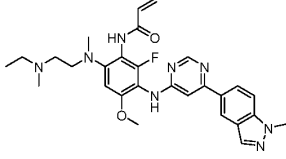
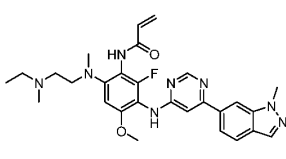
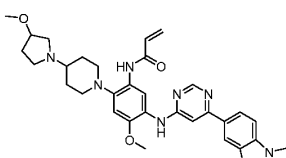
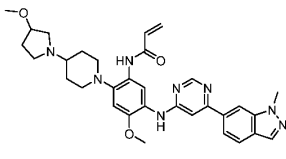
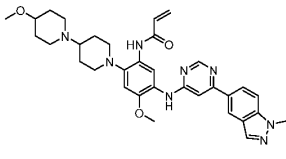
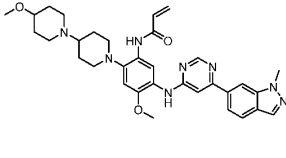
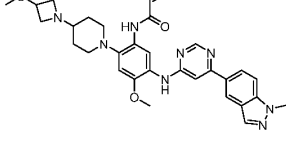
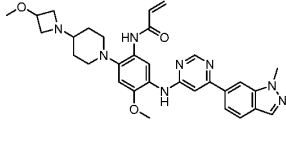
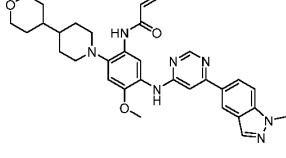
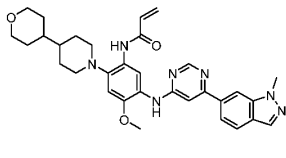
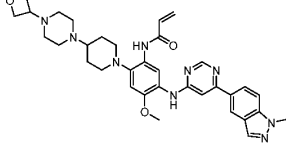
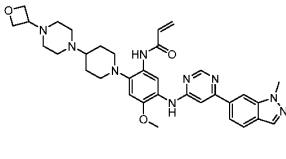
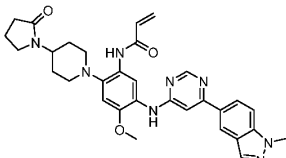
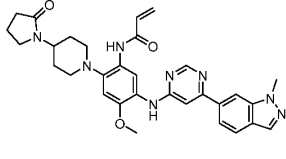
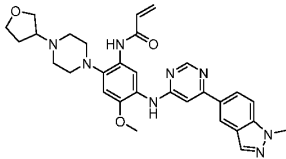
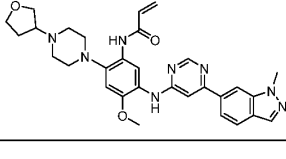
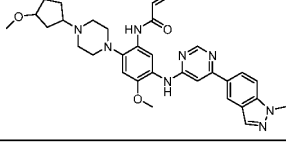
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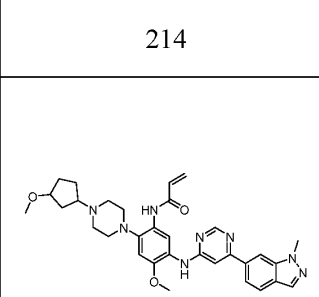
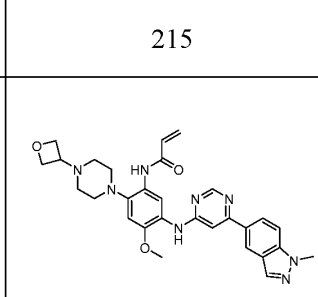
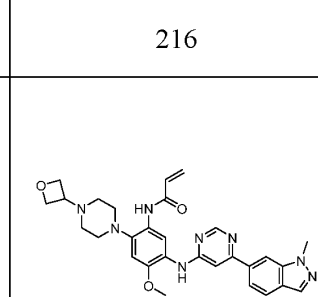
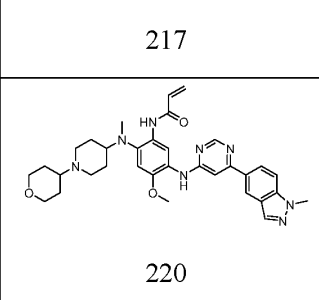
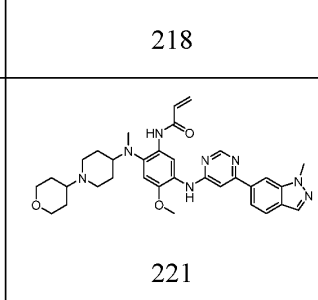
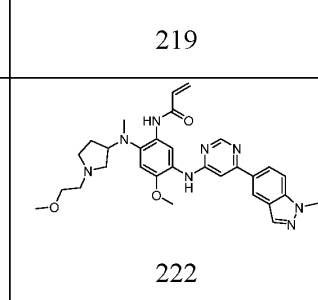
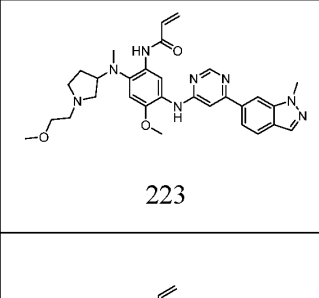
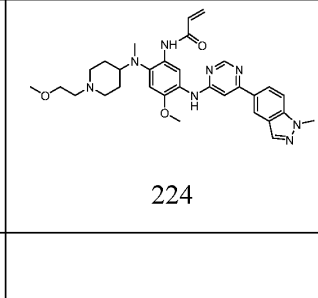
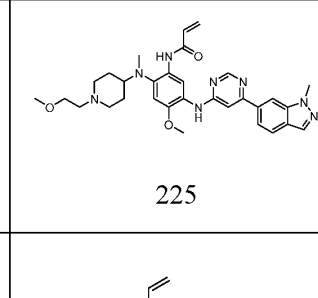
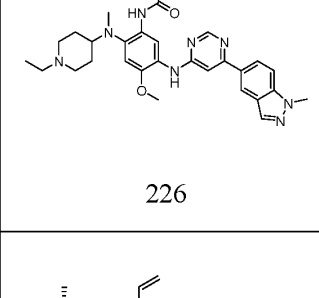
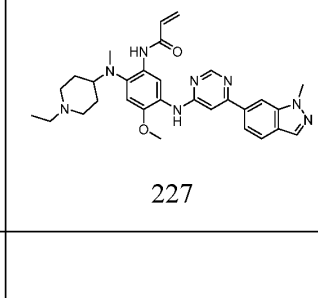
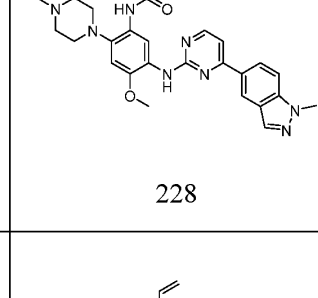
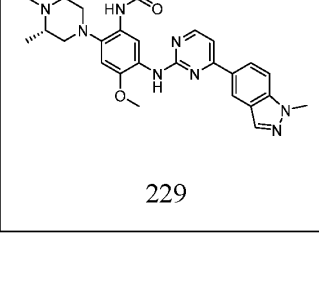
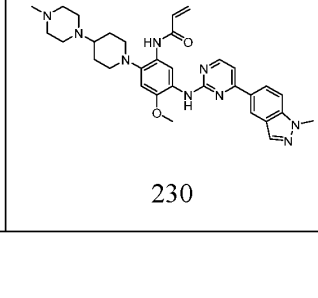
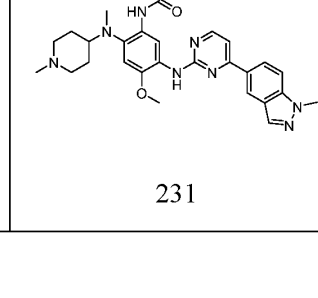
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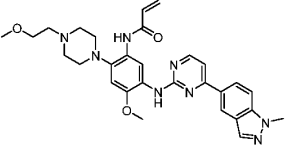
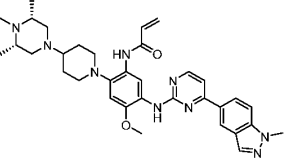
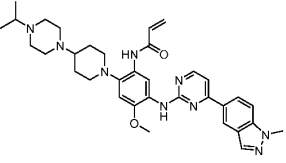
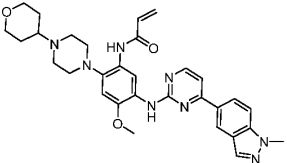
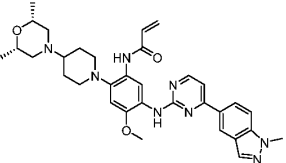
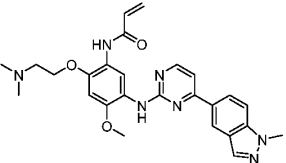
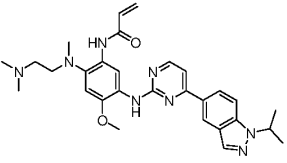
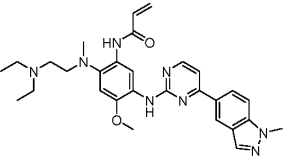
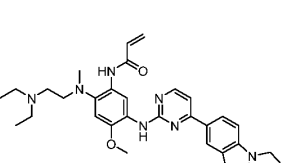
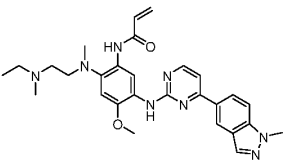
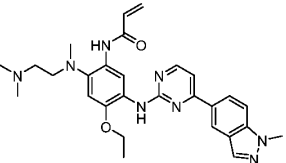
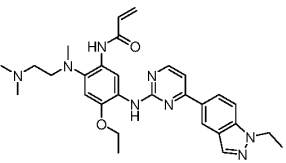
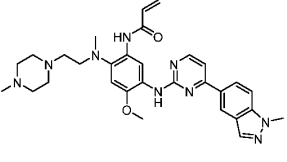
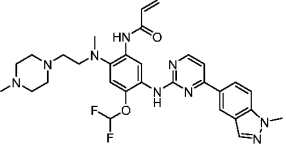
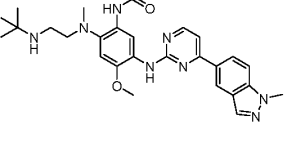
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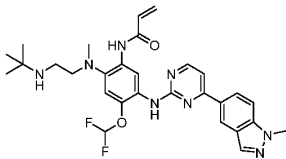
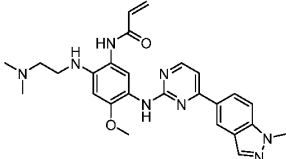
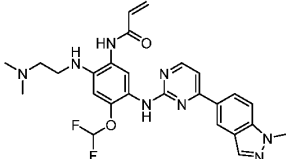
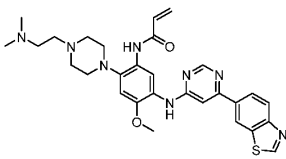
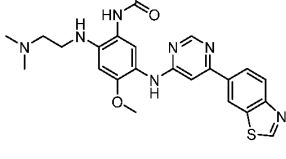
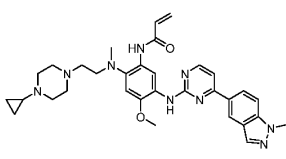
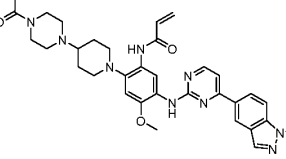
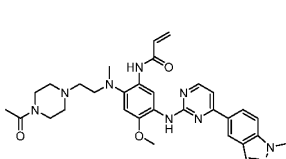
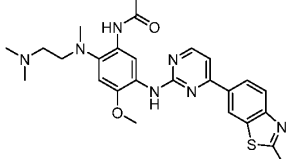
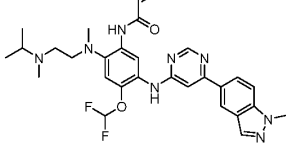
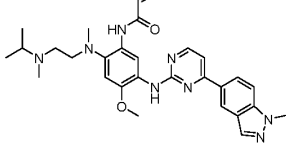
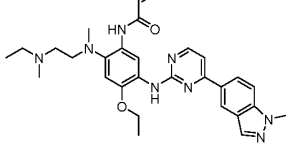
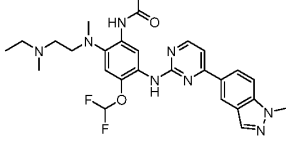
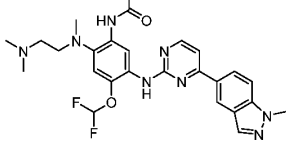
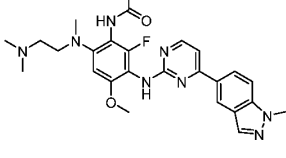
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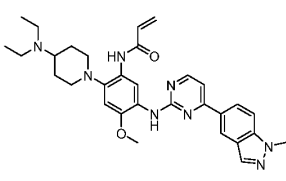
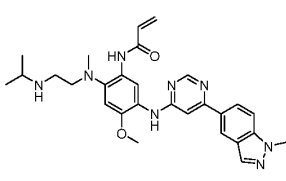
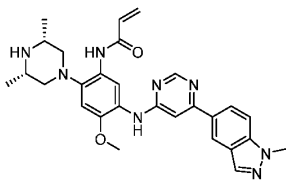
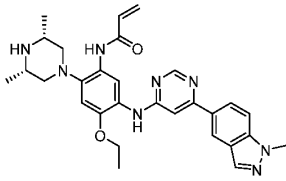
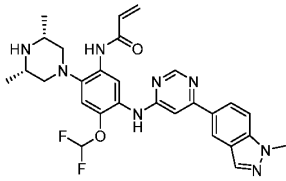
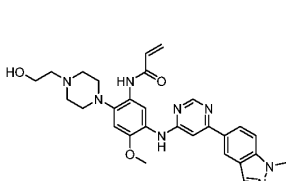
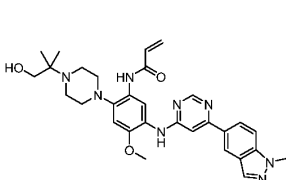
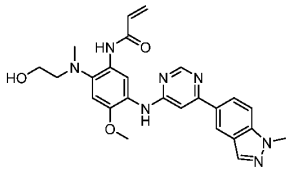
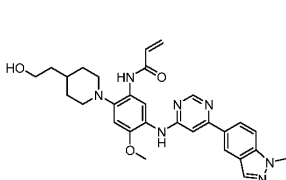
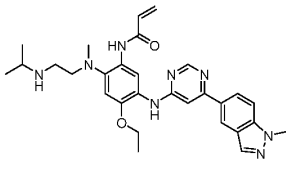
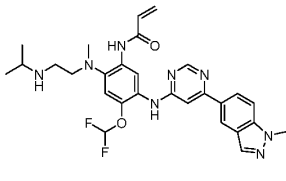
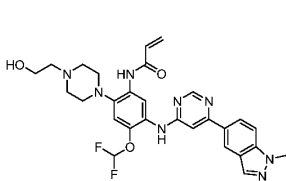
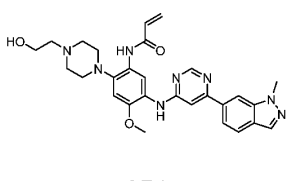
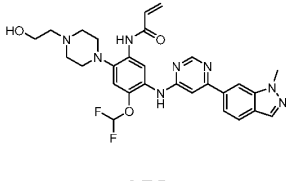
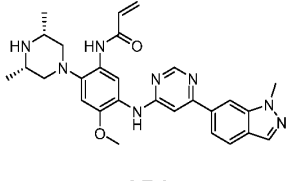
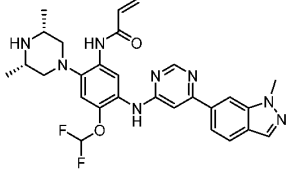
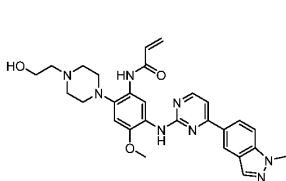
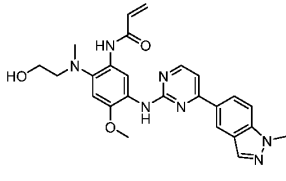
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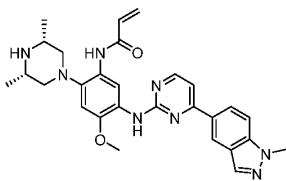
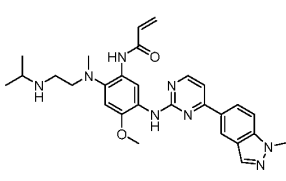
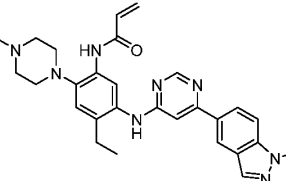
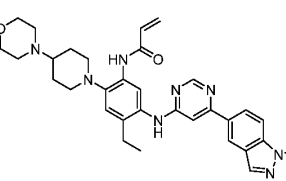
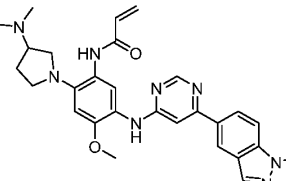
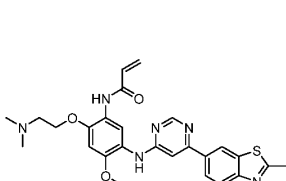
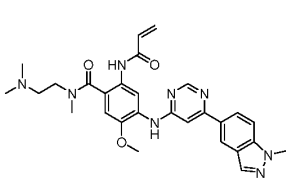
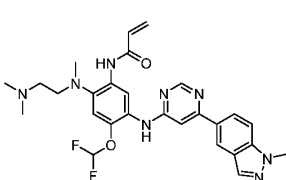
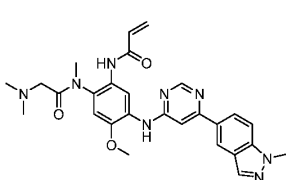
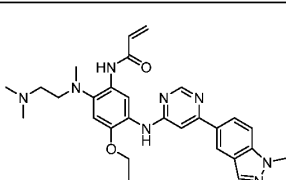
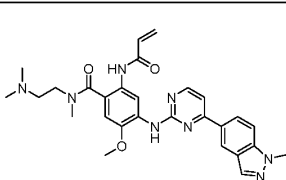
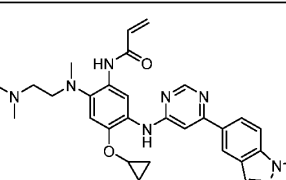
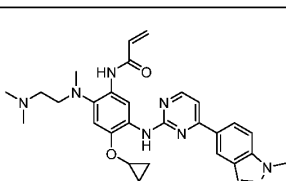
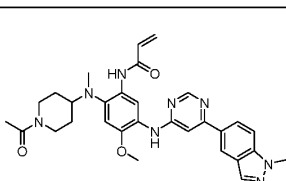
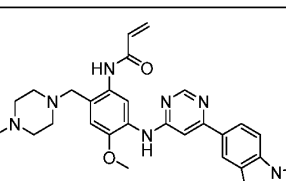
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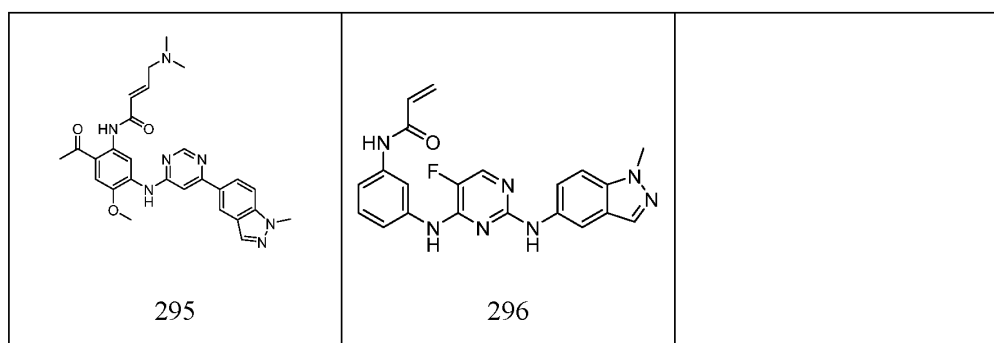
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实施例 446: 细胞增殖抑制实验

本实验采用 celltiter-Glo (CTG) 法测量前述制备的化合物在 3 个肿瘤细胞株 NCI-H1975、PC-9 和 A-431 中增殖抑制作用, 并计算 50%抑制浓度 IC_{50} 。

5 1 实验设计

在所选细胞上测定化合物, 并设定溶媒对照, 共检测 9 个浓度, 每个浓度 3 个复孔。

2 试剂和耗材

1) 2.1 胎牛血清 FBS (GBICO, Cat#10099-141)

2) CellTiter-Glo® Luminescent Cell Viability Assay (Promega, Cat#G7572)

10 3) 96 孔透明平底黑壁板 (Corning®, Cat# 3340)

3 仪器

EnVision 多标记微孔板检测仪, PerkinElmer, 2104-0010A;

CO₂ 培养箱, Thermo Scientific, Model 3100 Series;

生物安全柜, Thermo Scientific, Model 1300 Series A2;

15 倒置显微镜, Olympus, CKX41SF;

冰箱, SIEMENS, KK25E76TL。

4 实验方法

第一天: 细胞培养和接种

- 1) 收获处于对数生长期的细胞并采用细胞计数仪进行细胞计数。用台盼蓝排斥法检测细胞活力, 确保各细胞系活力在 90%以上。
- 2) 用完全培养液稀释调整细胞浓度, 添加 90 μL 细胞悬液至 96 孔板(T0 板和待测药板)中使细胞密度达到指定的浓度。
- 3) 96 孔板中的细胞置于 37 $^{\circ}\text{C}$ 、5% CO_2 、95%湿度条件下培养过夜。

第二天: T0 读板

- 1) 向 T0 板中补入 10 μL 培养液。
- 2) 融化 CTG 试剂并平衡细胞板至室温 30 分钟。
- 3) 每孔加入等体积的 CTG 溶液。
- 4) 在定轨摇床上振动 2 分钟使细胞裂解。
- 5) 将细胞板放置于室温 10 分钟以稳定冷光信号。
- 6) 用 EnVision 读取冷光值。

加药

- 1) 药物稀释。将待测化合物溶解并分装, 进行梯度稀释, 得到 10 倍溶液。
- 2) 加药。在已接种细胞的 96 孔板中每孔加入 10 μL 药物溶液, 每个细胞浓度设置三个复孔。被测化合物在 A-431 上的最高浓度为 30 μM , 9 个浓度, 3 倍稀释; 在 NCI-H1975 及 PC-9 上的最高浓度为 1.111 μM , 9 个浓度, 3 倍稀释。
- 3) 培养。将已加药的 96 孔板中的细胞置于 37 $^{\circ}\text{C}$ 、5% CO_2 、95%湿度条件下继续培养 3 天, 分别进行 CTG 检测分析。

第三天: 终点读板

- 1) 融化 CTG 试剂并平衡细胞板至室温 30 分钟。
- 2) 每孔加入等体积的 CTG 溶液。
- 3) 在定轨摇床上振动 2 分钟使细胞裂解。
- 4) 将细胞板放置于室温 10 分钟以稳定冷光信号。
- 5) 用 EnVision 读取冷光值。

5 数据处理

使用 GraphPad Prism 5.0 软件分析数据, 利用非线性 S 曲线回归来拟合数据得出剂量-效应曲线, 并由此计算 IC₅₀ 值。

$$\text{细胞存活率(\%)} = (\text{Lum}_{\text{待测药}} - \text{Lum}_{\text{培养液对照}}) / (\text{Lum}_{\text{细胞对照}} - \text{Lum}_{\text{培养液对照}}) \times 100\%.$$

10 6 实验结果

表 8. 待测化合物在 NCI-H1975、PC-9 和 A-431 细胞系上的抑制作用

终产物	NCI-H1975 IC ₅₀ (nM)	PC-9 IC ₅₀ (nM)	A-431 IC ₅₀ (nM)	A-431/NCI-H1975 选择性
1	4.7	5.6	890.4	187.8
2	6.6	4.4	362.3	85.8
3	4.1	7.9	491.2	120.3
4	15.1	10.1	514.4	34.0
5	5.6	3.9	302.2	53.9
6	32.1	19.4	1720.1	53.7
7	11.1	10.7	129.3	11.6
8	3.5	27.3	872.5	251.1
9	52.6	36.2	766.8	14.6
10	47.3	27.7	1987.0	42.0
11	67.4	21.8	2139.9	31.7
12	53.1	56.9	4126.3	77.7
13	1.8	8.6	769.7	427.6

14	6.1	5.9	1146.8	188.0
15	21.6	12.7	1289.5	59.7
16	57.0	40.5	1546.3	27.1
17	22.2	16.9	1246.8	56.2
18	11.1	8.9	983.0	88.8
19	18.1	10.7	850.0	47.0
20	46.1	24.9	1565.2	33.9
21	46.4	29.6	2766.8	59.7
22	18.1	13.4	1055.8	58.3
23	13.7	9.0	617.3	45.0
24	11.8	8.1	1061.3	90.1
25	54.7	67.8	736.4	13.5
26	10.4	9.1	216.2	20.7
27	14.2	21.6	387.0	27.2
28	32.3	19.6	1427.4	44.2
29	55.7	79.9	1812.9	32.6
30	32.4	24.7	1353.4	41.8
31	52.7	45.6	1576.2	29.9
32	186.1	10.9	9327.6	50.1
33	5.6	8.2	812.8	145.7
34	26.3	10.7	1947.0	74.1
35	13.2	16.4	1593.8	120.8
36	31.4	22.0	1011.8	32.3
37	67.5	79.8	1724.7	25.5
38	75.9	89.7	3312.7	43.7
39	24.5	25.7	973.3	39.6
40	57.0	46.1	1965.0	34.5
41	20.4	10.6	611.8	30.0
42	25.8	34.6	686.4	26.6
43	29.8	16.7	1140.0	38.3
44	101.6	32.8	1597.6	15.7

45	136.9	23.6	2606.3	19.0
46	82.8	32.7	1251.2	15.1
47	49.0	34.0	670.9	13.7
48	67.2	49.7	1390.3	20.7
49	85.6	88.0	1471.8	17.2
50	59.2	47.5	1077.5	18.2
51	69.4	59.8	1446.7	20.8
52	41.7	39.0	614.9	14.7
53	151.2	67.9	1249.7	8.3
54	111.1	88.2	1309.7	11.8
55	32.2	3.6	585.9	18.2
56	112.8	56.7	1225.6	10.9
57	13.3	10.7	1422.3	107.3
58	8.8	6.9	1129.1	128.8
59	10.0	8.9	1265.1	126.1
60	10.6	9.6	2301.1	217.0
61	17.8	9.4	1618.2	91.0
62	33.5	15.7	1171.5	35.0
63	4.1	6.5	540.3	130.7
64	13.1	5.4	689.5	52.6
65	10.9	12.0	764.7	70.2
66	8.1	8.5	778.9	96.2
67	14.6	15.0	890.9	61.0
68	14.7	15.3	921.4	62.7
69	13.4	10.4	1827.2	136.8
70	17.6	14.7	1162.8	66.1
71	33.1	27.8	2559.6	77.3
72	45.2	29.7	1904.5	42.1
73	65.3	50.4	1025.4	15.7
74	31.9	10.6	1149.8	36.0
75	24.3	13.6	1500.3	61.7

76	87.3	57.9	9450.5	108.3
77	34.5	16.4	1154.9	33.5
78	61.8	47.8	1029.6	16.7
79	73.6	67.9	1104.5	15
80	43.0	35.9	586.2	13.6
81	28.7	26.4	1379.8	48.1
82	24.0	29.6	1094.2	45.6
83	67.2	77.9	1516.6	22.6
84	34.4	27.5	987.9	28.7
85	72.3	56.7	1835.8	25.4
86	91.6	76.4	1776.0	19.4
87	113.6	77.6	1958.0	17.2
88	6.1	7.2	987.2	161.8
89	19.9	14.8	954.3	48.0
90	26.5	15.5	1754.3	66.2
91	62.2	47.2	1322.8	21.3
92	9.3	13.1	763.9	82.1
93	20.5	18.5	854.2	41.7
94	47.8	55.7	2038.2	42.6
95	6.7	12.2	997.4	148.9
96	13.7	10.8	945.3	69
97	33.1	22.6	798.4	24.1
98	83.5	31.7	1064.3	12.7
99	9.8	43.2	886.4	90.4
100	5.7	15.3	653.7	114.7
101	7.3	19.5	632.7	86.7
102	14.1	12.5	986.4	70.0
103	8.0	19.2	648.2	81.0
104	6.0	14.2	543.6	90.6
105	14.6	17.9	778.3	53.3
106	96.9	NT	2017.4	20.8

107	16.5	17.8	1290.3	78.2
108	3.2	5.7	567.2	177.3
109	32.3	35.0	1432.7	44.4
110	8.0	6.9	598.6	74.8
111	18.0	16.8	947.7	52.7
112	9.0	9.7	654.1	72.7
113	56.6	45.6	1356.9	24.0
114	31.5	32.7	1477.9	46.9
115	5.3	9.0	532.8	100.5
116	9.1	8.2	654.2	71.9
117	11.3	11.2	678.9	60.1
118	19.9	23.6	1057.8	53.2
119	23.1	17.8	1247.9	54.0
120	8.2	6.7	598.2	73.0
121	40.2	31.1	2314.7	57.6
122	5.2	11.6	579.6	111.5
123	13.7	15.5	698.3	51.0
124	35.2	32.3	1466.8	41.7
125	32.1	22.1	1577.9	49.2
126	85.0	64.1	2011.7	23.7
127	45.1	163.2	2301.2	51.0
128	103.4	70.7	1369.7	13.2
129	8.0	13.1	746.2	93.3
130	56.6	43.2	2314.7	40.9
131	9.6	14.8	578.3	60.2
132	42.3	118.3	2044.6	48.3
133	9.9	10.7	598.3	60.4
134	33.8	31.1	1432.7	42.4
135	15.4	17.7	756.4	49.1
136	56.2	45.6	2302.7	41.1
137	4.8	7.6	597.4	124.5

138	16.8	12.3	945.8	56.3
139	43.1	57.9	1156.0	26.8
140	11.7	13.8	987.3	84.4
141	8.4	23.1	539.4	64.2
142	24.5	32.6	967.9	39.5
143	51.6	23.5	988.2	19.2
144	6.8	16.4	572.1	84.1
145	37.1	33.7	1456.2	39.3
146	10.2	14.9	800.3	78.5
147	18.4	24.7	978.3	53.2
148	28.7	31.9	1346.7	46.9
149	28.4	674.2	1368.9	48.2
150	5.3	19.3	543.1	102.5
151	58.9	79.9	2045.7	34.7
152	23.6	43.2	1966.7	83.3
153	25.0	35.1	1324.5	53.0
154	34.7	36.4	1400.3	40.4
155	13.6	6.0	873.5	64.2
156	25.1	2.7	1243.7	49.5
157	32.7	11.0	1654.3	50.6
158	9.4	4.9	680.3	72.4
159	31.9	27.9	1534.7	48.1
160	39.2	32.7	2078.3	53.0
161	17.4	19.9	1032.4	59.3
162	16.8	18.9	762.8	45.4
163	18.5	13.8	834.4	45.1
164	12.6	23.2	590.7	46.9
165	50.0	40.7	2647.8	53.0
166	16.0	8.9	986.2	61.6
167	16.5	17.1	1046.7	63.4
168	6.8	21.5	584.1	85.9

169	34.3	11.4	1643.8	47.9
170	37.4	28.0	1648.9	44.1
171	26.2	38.0	743.3	28.4
172	18.6	16.3	953.6	51.3
173	22.7	7.3	1054.8	46.5
174	23.5	15.4	1325.7	56.4
175	8.1	26.0	793.4	98.0
176	21.2	4.8	1078.3	50.9
177	19.0	23.5	1468.4	77.3
178	42.9	34.6	2001.4	46.7
179	16.2	2.9	983.7	60.7
180	25.1	3.8	893.5	35.6
181	45.8	21.4	1679.4	36.7
182	53.3	55.9	1735.6	32.6
183	40.4	69.8	984.3	24.4
184	49.5	32.6	1056.2	21.3
185	53.8	43.7	2031.7	37.8
186	76.1	50.2	2567.8	33.7
187	53.0	46.8	2407.2	45.4
188	113.8	55.9	2789.3	24.5
189	108.6	24.1	2643.8	24.3
190	107.7	24.7	2077.1	19.3
191	91.8	56.4	1760.9	19.2
192	47.0	33.0	1843.3	39.2
193	52.8	30.9	1479.3	28.0
194	75.2	45.8	1637.9	21.8
195	20.4	19.5	1437.6	70.5
196	36.4	20.7	2017.3	55.4
197	20.7	13.4	1347.9	65.1
198	77.1	65.8	2344.7	30.4
199	37.8	24.7	1977.8	52.3

200	14.2	27.0	983.5	69.3
201	24.5	21.1	1344.7	54.9
202	10.7	12.7	798.3	74.6
203	8.1	7.2	982.1	121.2
204	15.7	15.8	890.7	56.7
205	13.0	7.6	884.7	68.1
206	8.1	12.1	773.0	95.4
207	10.2	5.6	894.8	87.7
208	20.0	10.7	1097.4	54.8
209	24.7	12.0	1623.9	65.7
210	10.4	11.7	983.0	94.5
211	11.3	7.4	1035.2	91.6
212	71.8	54.7	2033.5	28.3
213	74.9	55.6	2055.8	27.4
214	19.7	16.7	1529.0	77.6
215	18.4	15.4	1437.7	78.1
216	13.6	12.8	1224.2	90.0
217	16.9	13.6	1399.0	82.8
218	21.2	9.2	1834.9	86.6
219	49.4	45.9	2508.3	50.8
220	60.7	55.4	2433.6	40.1
221	70.3	96.0	2438.9	34.7
222	13.6	20.7	983.2	72.3
223	40.5	40.6	2322.7	57.4
224	15.8	27.1	1094.3	69.3
225	75.1	67.2	2468.9	32.9
226	68.2	54.6	2388.4	35.0
227	79.6	90.7	2437.8	30.6
228	65.7	35.7	1580.1	24.1
229	93.8	68.1	1624.6	17.3
230	68.2	59.4	1983.3	29.1

231	96.8	76.5	1727.4	17.8
232	90.2	82.7	2563.3	28.4
233	71.4	54.9	2437.2	34.1
234	80.1	32.7	2455.8	30.7
235	94.0	24.9	2399.4	25.5
236	60.0	38.7	2079.4	34.7
237	21.7	44.5	1824.6	84.1
238	51.6	99.4	1939.2	37.6
239	33.0	67.9	1577.9	47.8
240	62.0	110.4	2978.3	48.0
241	22.9	210.6	1037.4	45.3
242	26.7	28.1	1200.3	45.0
243	42.9	65.4	2178.3	50.8
244	59.7	84.7	2400.3	40.2
245	61.6	70.7	2378.3	38.6
246	89.7	67.2	2298.0	25.6
247	37.1	37.4	2988.3	80.5
248	13.3	27.7	2849.6	214.3
249	8.6	61.0	943.1	109.7
250	12.5	12.7	1023.6	81.9
251	12.5	7.0	1102.3	88.2
252	187.5	25.5	2993.6	16.0
253	62.2	32.1	2489.3	40.0
254	131.9	30.9	2274.4	17.2
255	46.4	30.0	2013.4	43.4
256	9.6	19.2	992.1	103.3
257	58.6	42.7	2067.4	35.3
258	51.6	32.4	2946.3	57.1
259	14.9	19.9	1528.3	102.6
260	12.8	20.1	1324.6	103.5
261	37.0	40.8	2100.4	56.8

262	123.5	52.7	2978.3	24.1
263	9.1	18.5	1200.5	131.9
264	5.5	22.1	923.5	167.9
265	20.6	34.7	1624.7	78.9
266	10.1	24.8	938.2	92.9
267	16.1	29.3	1036.8	64.4
268	27.1	15.6	1700.2	62.7
269	21.6	16.3	1573.9	72.9
270	44.4	54.6	2403.2	54.1
271	25.2	77.7	2391.0	94.9
272	5.6	13.9	987.2	176.3
273	53.3	79.8	2678.3	50.2
274	47.0	56.7	2038.9	43.4
275	136.0	43.2	3302.1	24.3
276	32.4	13.0	2108.3	65.1
277	52.9	21.9	2006.6	37.9
278	117.1	40.9	2478.9	21.2
279	25.7	21.4	2899.1	112.8
280	99.4	87.4	3217.6	32.4
281	72.0	67.9	3327.8	46.2
282	22.7	32.7	1370.3	60.4
283	37.3	46.9	1519.7	40.8
284	26.3	13.4	670.2	25.5
285	40.6	23.1	632.7	15.6
286	40.1	30.9	803.6	20.0
287	4.0	9.2	611.8	152.9
288	98.2	76.7	1924.5	19.6
289	12.2	24.1	1037.9	85.1
290	30.8	36.5	1629.3	52.9
291	89.5	54.3	2734.5	30.6
292	90.4	64.7	2978.4	32.9

293	79.6	54.2	2733.8	34.3
294	71.3	44.9	4581.8	64.2
295	32.5	27.9	3769.4	116.0
已知化合物 296	90.7	121	1442.6	15.9

注：NC 表示未计算；NT 表示未测试。

结论：本发明实施例终产物对 EGFR 突变型 NCI-H1975 细胞具有很强的抑制活性，对野生型 A-431 细胞抑制活性较低，对野生型/突变型细胞具有很好的选择性。

实施例 447: P-gp 底物评价实验

5 1. 试验设计

细胞培养

- 1) 使用含L-谷氨酰胺的高糖DMEM培养基，添加10%胎牛血清、0.1 mg/mL 链霉素和0.6 µg/mL青霉素。
- 2) MDCKII-MDR1培养于T-75细胞培养瓶。培养箱设置为37 °C、5% CO₂、保证相对湿度95%。细胞汇合度达到70 - 90%时可用于接种Transwell。
- 3) 细胞接种前，向Transwell上室每孔中加入50 µL细胞培养基，下层培养板内加入25 mL细胞培养基。将培养板置于37 °C，5% CO₂培养箱内孵育1小时后可用于接种细胞。
- 4) 使用5 mL PBS轻轻清洗细胞。弃掉PBS，加入1.5 mL含EDTA的胰酶，于37 °C 孵育5到10分钟至细胞完全脱落。加入含血清的培养基终止消化。
- 5) 吸取细胞混悬液转移至圆底离心管，于120×g离心10分钟。
- 6) 使用培养基重悬细胞，终浓度为 1.56×10^6 cells/mL。

MDCKII-MDR1 细胞接种

1) 将细胞悬液以 50 μL 每孔加入到 96 孔 Transwell 培养板上室中, 最终接种密度为 $5.45 \times 10^5 \text{ cells/cm}^2$ 。

2) 接种后48小时开始换液, 培养4-7天, 隔一天换一次培养基。

细胞单层膜完整性的评价

5 1) MDCKII-MDR1 和 MDCKII 经过 4-7 天培养后, 应完全汇合并完成分化。此时, 可应用于穿透试验。

2) 用电阻仪 (Millipore, USA) 测量单层膜电阻, 记录每孔电阻。

3) 测定结束后, 将Transwell培养板放回培养箱。

4) 电阻值的计算:

10 测定电阻值(ohms) x 膜面积 (cm^2) = TEER值 ($\text{ohm} \cdot \text{cm}^2$)

若TEER值 $< 42 \text{ ohms} \cdot \text{cm}^2$, 则该孔不能用于穿透试验。

药物穿透试验

1) 从培养箱中取出MDCKII-MDR1 Transwell培养板。使用HBSS (25 mM HEPES, pH 7.4) 缓冲液润洗细胞单层膜两次, 37 $^{\circ}\text{C}$ 条件下孵育30分钟。

15 2) 测定化合物由顶端到基底端的转运速率。向上层小室 (顶端) 每孔加入100 μL 含TA或对照药的HBSS (25 mM HEPES, pH 7.4) 缓冲液, 下层小室 (基底端) 每孔加入300 μL HBSS (25 mM HEPES, pH 7.4) 缓冲液。

3) 测定化合物由基底端到顶端的转运速率。向上层小室(顶端)每孔加入100 μL HBSS (25 mM HEPES, pH 7.4) 缓冲液, 下层小室 (基底端) 每孔加入300 μL 含TA或对

20 照药的HBSS (25 mM HEPES, pH 7.4) 缓冲液。

4) 将上下的转运装置合并后, 37 $^{\circ}\text{C}$ 条件下孵育2小时。

- 5) 孵育完成后, 分别从Transwell培养板上室和下室每孔取样80 μL 加入到新的样品管中。向样品管内加入3倍体积含内标的乙腈(200 nM 阿普唑仑, 200 nM 拉贝洛尔, 200 nM 双氯芬酸, 100 nM 甲苯磺丁脲), 涡旋5分钟后, 于4,000 g离心15分钟。吸取上清液70 μL , 与等体积水稀释之后进行LC-MS/MS分析。所有样品进行三平行制备。
- 6) 用荧光黄的渗漏评价孵育2小时后细胞单层膜的完整性, 使用HBSS (25 mM HEPES, pH 7.4) 稀释荧光黄储备液至最终浓度100 μM 。在上侧的Transwell插板的每个孔中加入荧光黄溶液100 μL , 下侧接收板的每个孔中加300 μL HBSS (25 mM HEPES, pH 7.4)。37 $^{\circ}\text{C}$ 下孵育30分钟后, 分别从每孔上下层吸出80 μL 溶液至一个新的96孔板中。使用酶标仪, 激发波长485 nm和发射波长530 nm条件下进行荧光测定。

2.数据处理

数据计算均使用 Excel 进行, 化合物的表观渗透系数 (P_{app} , 单位: cm/s) 用以下公式计算得出:

$$\text{表观渗透系数} = \frac{\text{接收端溶液的体积}}{\text{膜面积} \times \text{孵育时间}} \times \frac{\text{接收端药物浓度}}{\text{给药端初始药物浓度}}$$

- 15 公式中膜面积为Transwell- 96孔板膜面积 (0.143 cm^2); 孵育时间单位为秒 (s)。

外排率使用以下的公式计算得出:

$$\text{外排率} = \frac{\text{基底端到顶端的表观渗透系数}}{\text{顶端到基底端的表观渗透系数}}$$

表 9. 待测化合物的外排率

终产物	ER (外排率, Efflux Ratio)
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1	4.04
2	2.19
3	5.87
5	12.2
8	3.14
13	31.23
23	4.28
24	1.05
26	5.79
27	1.67
33	7.70
34	6.12
35	9.19
42	3.69
55	2.71
57	5.30
58	49.19
59	46.97
60	6.49
61	22.12
62	2.44
68	8.98
70	41.43
99	1.54
100	20.01
101	15.09
103	2.28
104	3.12
108	18.09
110	7.28
115	41.93

116	67.93
129	55.66
131	51.68
135	55.84
137	7.83
138	2.17
144	11.57
154	1.25
155	0.93
158	15.27
159	1.12
164	34.38
166	11.69
167	29.86
168	23.14
172	43.87
173	32.19
176	3.98
179	17.13
180	3.07
200	65.23
203	6.51
205	4.29
206	5.87
210	11.40
211	8.33
250	15.79
251	42.64
264	15.50
267	14.64