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(54)发明名称

杂环衍生物

(57)摘要

本发明提供一种各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的新型且优良的预防或治疗方法，该方法基于PI3Kδ选择性抑制作用和/或IL-2产生抑制作用和/或B细胞增殖抑制作用(包括活化抑制作用)。本发明人发现，三取代三嗪或三取代嘧啶衍生物显示出PI3Kδ选择性抑制作用和/或IL-2产生抑制作用和/或B细胞增殖抑制作用(包括活化抑制作用)，可作为各种脏器移植中的排斥反应、变应性疾病(哮喘、特应性皮炎等)、自身免疫疾病(类风湿性关节炎、牛皮癣、溃疡性结肠炎、克罗恩病、全身性红斑狼疮等)或血液肿瘤(白血病等)等的预防或治疗剂，从而完成了本发明。

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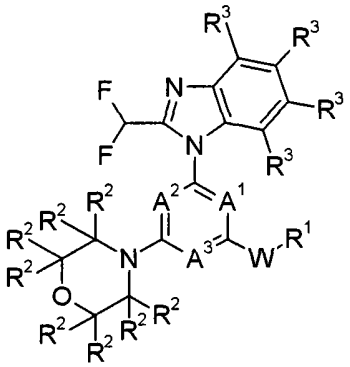
1. 式 (I) 的化合物或其盐；



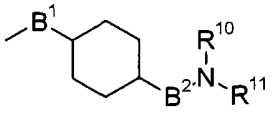
(I)

式中，

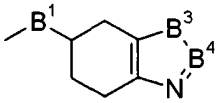
A^1、A^2 及 A^3：相同或彼此不同，为 CH 或 N，其中 A^1 ～ A^3 中的两个以上为 N；

W：NH 或 O；

R^1：



或



；

R^2：相同或彼此不同，为 H 或者可被卤素或 -OH 取代的低级烷基；

R^3：相同或彼此不同，为 H 或卤素；

B^1：键或 C_{1-4} 亚烷基；

B^2：键或 C_{1-4} 亚烷基；

B^3：O、S 或 NR^0；

B^4：CR^{12} 或 N；

R^0：相同或彼此不同，为 H 或低级烷基；

R^{10}：H；低级烷基，这里的所述低级烷基可被卤素、-C(O)O- 低级烷基、-OH 或 -O- 低级烷基取代；低级烯基；低级炔基；- 低级亚烷基 - 苯基，这里的所述苯基可被 -O- 低级烷基取代；- 低级亚烷基 -O- 低级亚烷基 - 苯基；

R^{11}：H、R^{100}、$-C(O)R^{101}$、$-C(O)OR^{102}$、$-C(O)NR^{103}R^{104}$ 或 $-S(O)_2R^{105}$；

或者 R^{10} 及 R^{11} 与它们所结合的 N 一起形成含有 1 ～ 4 个选自 O、S 和 N 的杂原子的三～八元的单环杂环基，该单环杂环可被下述基团取代：可被卤素或 OH 或 -O- 低级烷基或杂环取代的低级烷基、氧代基、-C(O)O- 低级烷基、$N(R^0)_2$、卤素、-CN、-OH、-O- 低级烷基、-O-C(O)- 低级烷基、-O- 低级亚烷基 - 苯基或杂环基；

R^{12}：R^0 或氨基；

R^{100}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：卤素、$-C(O)N(R^0)_2$、-C(O)O- 低级烷基、-CN、-OH、-O- 低级烷基、-O- 低级亚烷基 - 苯基、-NHC(O)O- 低级亚烷基 - 苯基及 $-S(O)_2$- 低级烷基；低级烯基；低级炔基；

-X- 环烷基，这里的所述环烷基可被选自下述基团的基团取代：低级烷基、苯基、- 低级亚烷基 -O- 低级烷基、-O- 低级烷基及 - 低级亚烷基 - 苯基，这里的所述苯基可被 -O- 低级烷基取代；

-X- 芳基，这里的所述芳基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、-CN、-OH、-O- 低级烷基、-O- 卤代低级烷基、-O- 低级亚烷基 -OH、-O- 低级亚烷基 - 苯基、$-S(O)_2-$ 低级烷基、$-N(R^0)_2$、吡咯烷基、可被 OH 取代的哌啶基、吗啉基及三唑基；或

-X- 杂环基，这里的所述杂环基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、吗啉基、-C(O)O- 低级亚烷基 - 苯基、-OH、- 低级亚烷基 - 苯基及 - 低级亚烷基 -OH；

R^{101}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：卤素，$-C(O)N(R^0)_2$，-C(O)- 哌嗪基、这里的所述哌嗪基可被 - 低级亚烷基 -OH 取代，-CN，-OH，-O- 低级烷基，-O- 低级亚烷基 - 苯基，-O- 低级亚烷基 -O- 低级烷基，-O-（可被 -CN 取代的苯基），$-S(O)_2-$ 低级烷基，$-S(O)_2-$ 苯基，$-N(R^0)_2$，$-N(R^0)-$ 低级烷基、这里的所述低级烷基可被 -O- 低级烷基取代，-NH- 苯基，-NHC(O)- 低级烷基，-NHC(O)- 苯基，-NHC(O)-（可被 -OH 取代的吡啶基），$-N(R^0)C(O)O-$ 低级烷基，-NHC(O)O- 低级亚烷基 - 苯基，$-NHS(O)_2-$ 苯基、这里的所述苯基可被选自低级烷基及卤素的基团取代，以及 $-NHS(O)_2-$ 噻吩基；

-X- 环烷基，这里的所述环烷基可被选自下述基团的基团取代：苯基、-CN、-OH、-O- 低级烷基及 - 低级亚烷基 -OH；

-X- 苯基，这里的所述苯基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、-C(O)O- 低级烷基、-CN、-OH、-O- 低级烷基、$-N(R^0)_2$、$-N(R^0)-$ 低级亚烷基 -OH、$-N(-$ 低级亚烷基 $-OH)_2$、-NHC(O)- 低级烷基、$-N(R^0)C(O)N(R^0)_2$、$-S(O)_2-$ 低级烷基、$-S(O)_2N$（低级烷基）$_2$、- 低级亚烷基 -OH、- 低级亚烷基 -O- 低级烷基、-X- 哌啶基、-X- 吗啉基及 -X-（可被低级烷基取代的哌嗪基）；

-X- 杂环基，这里的所述杂环基可被选自下述基团的基团取代：低级烷基、卤素、-OH、卤代低级烷基、苯基、-C(O)O- 低级烷基、-C(O)O- 低级亚烷基 - 苯基、-C(O)-（可被 -OH 取代的吡啶基）、-C(O)- 低级烷基、氧代基、$-N(R^0)_2$、$-N(R^0)C(O)O-$ 低级烷基、$-S(O)_2-$ 苯基、可被低级烷基取代的哌啶基、-X- 吡啶基、- 低级亚烷基 - 苯基、- 低级亚烷基 -OH、- 低级亚烷基 -O- 低级烷基及 - 低级亚烷基 -（可被低级烷基取代的吡唑基）；或者

$-C(O)N(R^0)_2$；

R^{102}：低级烷基；

R^{103}：H 或低级烷基；

R^{104}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：-CN、-OH、-O- 低级烷基或 $-N(R^0)_2$；

-X- 苯基，这里的所述苯基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、-CN、-O- 低级烷基、-O- 卤代低级烷基及 $-N(R^0)_2$；或

-X- 杂环基；

或者 R^{103} 及 R^{104} 与它们所结合的 N 一起形成吗啉基；

R^{105}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：卤素、-O- 苯基或

杂环基，这里的所述苯基可被 -O- 低级烷基取代；低级烯基；-X- 环烷基；

-X- 芳基，这里的所述芳基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、-C(O)O- 低级烷基、$-C(O)N(R^0)_2$、-CN、-C(O)- 低级烷基、-C(O)- 吡啶基、-O- 低级烷基、-O- 卤代低级烷基、-O- 环烷基、-O- 苯基、-O- 低级亚烷基 -CN、-X-NHC(O)- 低级烷基、-NHC(O)- 吗啉基、$-S(O)_2$- 低级烷基、$-N(R^0)C(O)N(R^0)_2$、$-S(O)_2N(R^0)_2$ 及 $-S(O)_2$- 吗啉基；

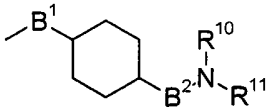
-X- 杂环基，这里的所述杂环基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、-C(O)- 低级烷基、-C(O)- 卤代低级烷基、-C(O)- 环烷基、-O- 低级烷基、-O- 苯基、氧代基、-NHC(O)- 低级烷基、吗啉基及异噁唑基；或者

$-N(R^0)_2$；

X：键或低级亚烷基。

2. 权利要求 1 所述的化合物或其盐，其特征在于，A^1 为 CH 且 A^2 及 A^3 为 N、或者 A^2 为 CH 且 A^1 及 A^3 为 N。

3. 权利要求 2 所述的化合物或其盐，其特征在于，R^1 为



4. 权利要求 3 所述的化合物或其盐，其特征在于，B^1 为键或亚甲基，B^2 为键。

5. 权利要求 4 所述的化合物或其盐，其特征在于，R^2 相同或彼此不同，为 H 或低级烷基。

6. 权利要求 5 所述的化合物或其盐，其特征在于，R^3 为 H。

7. 权利要求 6 所述的化合物或其盐，其特征在于，R^{10} 为 H、可被卤素或 -OH 取代的低级烷基、- 低级亚烷基 -O- 低级烷基、低级烯基、低级炔基、- 低级亚烷基 - 苯基或 - 低级亚烷基 -O- 低级亚烷基 - 苯基，这里的所述苯基可被 -O- 低级烷基取代。

8. 权利要求 7 所述的化合物或其盐，其特征在于，R^{11} 为 R^{100} 或 $-C(O)R^{101}$。

9. 权利要求 6 所述的化合物或其盐，其特征在于，R^{10} 及 R^{11} 与它们所结合的 N 一起形成含有 1 ～ 4 个选自 O、S 和 N 的杂原子的三～八元的单环杂环基，该单环杂环可被选自低级烷基、氧代基、卤代低级烷基、- 低级亚烷基 -OH、-C(O)O- 低级烷基、$-C(O)NR^{103}R^{104}$、$N(R^0)_2$、卤素、-CN、-OH、-O- 低级烷基、- 低级亚烷基 -O- 低级烷基或杂环基取代。

10. 权利要求 1 所述的化合物或其制药学上可接受的盐，其特征在于，选自下组：

N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氧基) 环己基]-N, N- 二甲基甘氨酰胺、

N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基]-N, N- 二甲基甘氨酰胺、

4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-({ 反 -4-[(2- 氟乙基)(甲基) 氨基] 环己基 } 甲基)-6- 吗啉 -4- 基嘧啶 -2- 胺、

4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-({ 反 -4-[(2- 甲氧基乙基)(甲基) 氨基] 环己基 } 甲基)-6- 吗啉 -4- 基嘧啶 -2- 胺、

6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基 -N-[(反 -4- 吗啉 -4- 基环己基) 甲基] 嘧啶 -4- 胺、

1-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3S)-3-甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}(甲基)氨基]-2-甲基丙烷-2-醇、

1-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3S)-3-甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}(乙基)氨基]-2-甲基丙烷-2-醇、

4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[乙基(1-甲氧基丙烷-2-基)氨基]环己基}甲基)-6-(吗啉-4-基)嘧啶-2-胺、

4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-{[反-4-(二丙基氨基)环己基]甲基}-6-(吗啉-4-基)嘧啶-2-胺、

3-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-(吗啉-4-基)嘧啶-2-基}氨基)甲基]环己基}(甲基)氨基]-2-甲基丁烷-2-醇、

6-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(3S)-3-氟吡咯烷-1-基]环己基}甲基)-2-(吗啉-4-基)嘧啶-4-胺、

3-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3S)-3-甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}(甲基)氨基]-2-甲基丁烷-2-醇、

3-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}(甲基)氨基]-2-甲基丁烷-2-醇、

4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(1-甲氧基丙烷-2-基)(甲基)氨基]环己基}甲基)-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-胺、

4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[乙基(1-甲氧基丙烷-2-基)氨基]环己基}甲基)-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-胺、

4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2S)-2-(氟甲基)吡咯烷-1-基]环己基}甲基)-6-(吗啉-4-基)嘧啶-2-胺、及

6-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2S)-2-(氟甲基)氮杂环丁烷-1-基]环己基}甲基)-2-(吗啉-4-基)嘧啶-4-胺。

11. 一种药物组合物，该药物组合物含有权利要求1所述的化合物或其盐及制药学上可接受的赋形剂。

12. 各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗用药物组合物，该药物组合物含有权利要求1所述的化合物或其盐。

13. 权利要求1所述的化合物或其盐在制造用于预防或治疗各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病或血液肿瘤等的药物组合物中的用途。

14. 权利要求1所述的化合物或其盐在用于预防或治疗各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病或血液肿瘤等中的用途。

15. 各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病或血液肿瘤等的预防或治疗方法，该方法包括给予患者有效量的权利要求1所述的化合物或其制药学上可接受的盐。

杂环衍生物

技术领域

[0001] 本发明涉及一种具有药理活性的杂环衍生物和/或其盐。本发明还涉及包含上述杂环衍生物和/或其盐作为活性成分的药物或药物组合物。

背景技术

[0002] 磷脂酰肌醇-3-激酶(PI3K)是普遍存在于从植物、酵母到以人为代表的哺乳类的各种物种内的脂质信号传导激酶(lipid signaling kinase)。PI3K是将作为细胞膜磷脂的磷脂酰肌醇、磷脂酰肌醇-4-磷酸及磷脂酰肌醇-4,5-二磷酸的3位羟基磷酸化的酶,由各底物分别生成磷脂酰肌醇-3-磷酸、磷脂酰肌醇-3,4-二磷酸及磷脂酰肌醇-3,4,5-三磷酸(PIP3)。这些生成的磷酸化磷脂酰肌醇起到细胞内第二信使的作用。特别是PIP3使具有血小板-白细胞C激酶底物同系(Pleckstrin homology,PH)结构域的各种分子迁移至细胞膜附近,诱导这些分子的活化,因此被认为是最重要的磷酸化磷脂酰肌醇(" The Journal of Biological Chemistry",1999年,第274卷,8347-8350页)。

[0003] PI3K根据各种特征可分为Class I、II、III三类,而在机体内产生PIP3的唯一的酶是Class I PIP3,因此Class I PIP3被认为是最重要的一类(" Biochimica et Biophysica Acta",2008年,第1784卷,159-185页)。Class I PIP3还可分为IA和IB。Class IA PI3K由异源二聚体构成,该异源二聚体由110kDa的催化亚基(p110α、β或δ)和50～85kDa的调节亚基(p85α、p85β、p55α、p55γ或p50α)的组合形成;Class IB PI3K是110kDa的催化亚基(p110γ)和101kDa的调节亚基(p101)的异源二聚体(" Nature Immunology",2003年,第4卷,313-319页)。以下,将各PI3K的名称与它们所包含的催化亚基相对应地记作PI3Kα、β、δ和γ。

[0004] 有报道称,PI3Kα和β广泛存在于机体内,缺失这些的小鼠均为胚胎致死(" The Journal of Biological Chemistry",1999年,第274卷,10963-10968页;" Mammalian Genome",2002年,第13卷,169-172页)。使用亚型选择性化合物的研究结果称,PI3Kα在胰岛素信号转导中起到重要的作用,PI3Kα抑制剂导致胰岛素抵抗(" Cell",2006年,第125卷,733-747页)。也有报道称,PI3Kβ参与血小板凝集,PI3Kβ抑制剂具有抗血栓作用(" Nature Medicine",2005年,第11卷,507-514页)。与之相对,PI3Kδ或γ缺失的小鼠均能正常出生,在生长、寿命及繁殖等方面也未见问题(" Science",2000年,第287卷,1040-1046页;" Molecular and Cellular Biology",2002年,第22卷,8580-8591页)。特别是PI3Kδ的表达局限性非常大,仅限于血细胞和淋巴组织,在PI3Kδ缺失的小鼠中可见淋巴细胞的显著的活化障碍。已知淋巴细胞的活化与免疫、炎症密切相关,选择性地抑制PI3Kδ的化合物有可能成为兼具强烈的淋巴细胞活化抑制作用和安全性的免疫、炎症抑制剂。

[0005] 白细胞介素2(IL-2)是主要由活化T细胞产生的细胞因子的一种。IL-2经由其受体即IL-2受体来诱导淋巴细胞的增殖及活化。IL-2在免疫系统的活化信号转导中是非常重要的分子,其产生抑制剂(例如他克莫司和环孢菌素A)在临床上被用作免疫抑制剂。巴

利昔单抗 (Basiliximab) 和达克珠单抗 (Daclizumab) 之类的抗 IL-2 受体单克隆抗体也在临床上被用作免疫抑制剂。

[0006] B 细胞是与 T 细胞相当的淋巴细胞的主要亚群之一，是成为体液免疫的主体的细胞。已知体液免疫在病原菌等的感染防御中起着极为重要的作用，但在类风湿性关节炎等自身免疫疾病中，发生体液免疫的异常活化，这与发病密切相关。在实际应用方面，抗 CD20 抗体利妥昔单抗 (Rituximab) 在临床上被用作针对类风湿性关节炎的治疗药。

[0007] 作为 PI3K δ 选择性抑制剂，报道了喹唑啉 -4- 酮衍生物（专利文献 1 ～ 3)，其对炎症、免疫疾病、血液肿瘤（白血病等）等显示出有用性。作为其它的 PI3K δ 选择性抑制剂，报道了噻唑基脲衍生物（专利文献 4)，其对炎症、免疫疾病等显示出有用性。

[0008] 作为三嗪和嘧啶衍生物，报道了下述化合物。专利文献 5 ～ 9 中揭示，式 (A) 的化合物具有抗肿瘤活性。专利文献 10 和非专利文献 1 中报道了式 (A) 的化合物在免疫系统细胞内的 PI3K 抑制作用，揭示了式 (A) 的化合物作为免疫抑制剂的有用性。但是，其中并未揭示本申请记载的化合物，也没有关于 PI3K δ 选择性抑制作用的详细记载。

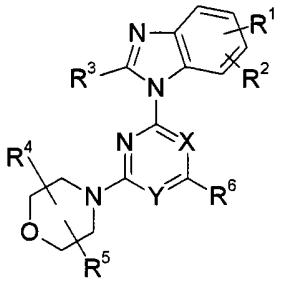
[0009] （式中，R^3 表示 H 或二氟甲基等，R^6 表示吗啉代基、哌啶子基等环状基团或者可被 C_{1-6} 烷基、羟基 C_{1-6} 烷基、吗啉代 C_{1-6} 烷基取代的氨基等。其余标记参照该公报）

[0010] 专利文献 11 ～ 22 中揭示，式 (B-1) ～ (B-4) 的化合物具有 PI3K 抑制作用。但是，其中并未揭示本申请记载的化合物，也没有关于 PI3K δ 选择性抑制作用的记载。

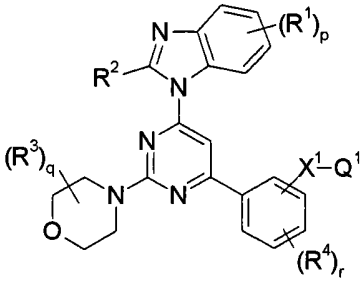
[0011] （式中的标记参照该公报）

[0012] 专利文献 23 和 24 中揭示，以式 (C) 表示的化合物具有 PI3K 抑制作用。但并未揭示本申请记载的化合物。

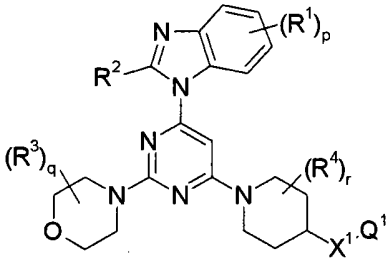
[0013]



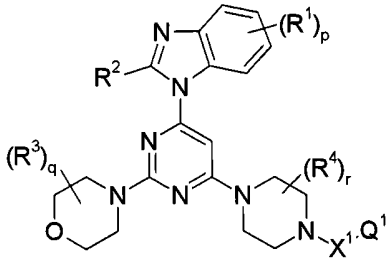
(A)



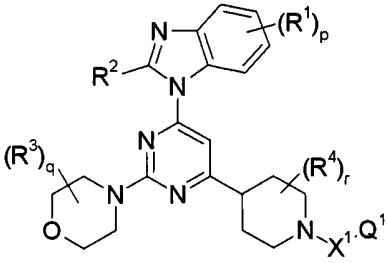
(B-1)



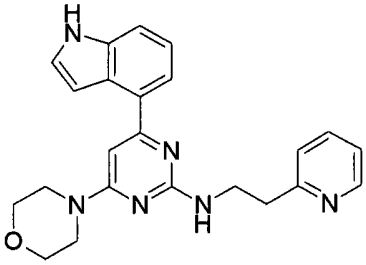
(B-2)



(B-3)



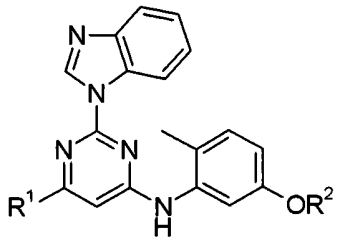
(B-4)



(C)

[0014] 非专利文献 2 中揭示，式 (D) 的仲胺化合物具有 Lck 抑制作用和 IL-2 产生抑制作用，提示了其在自身免疫疾病和脏器移植中的排斥反应中的应用。但没有关于 PI3K 抑制作用的记载。

[0015]



(D)

[0016] （式中，R^1 表示吗啉代基等，R^2 表示 H 或甲基）

[0017] 现有技术文献

[0018] 专利文献

[0019] 专利文献 1：国际公开第 01/81346 号小册子

[0020] 专利文献 2：国际公开第 03/035075 号小册子

[0021] 专利文献 3：国际公开第 2005/113556 号小册子

[0022] 专利文献 4：国际公开第 2008/000421 号小册子

[0023] 专利文献 5：欧洲专利申请公开第 1020462 号说明书

[0024] 专利文献 6：国际公开第 00/43385 号小册子

[0025] 专利文献 7：欧洲专利申请公开第 1389617 号说明书

[0026] 专利文献 8：欧洲专利申请公开第 1557415 号说明书

[0027] 专利文献 9：欧洲专利申请公开第 1741714 号说明书

[0028] 专利文献 10：欧洲专利申请公开第 1864665 号说明书

[0029] 专利文献 11：国际公开第 2008/032027 号小册子

[0030] 专利文献 12：国际公开第 2008/032028 号小册子

[0031] 专利文献 13：国际公开第 2008/032033 号小册子

[0032] 专利文献 14：国际公开第 2008/032036 号小册子

[0033] 专利文献 15：国际公开第 2008/032041 号小册子

[0034] 专利文献 16：国际公开第 2008/032060 号小册子

[0035] 专利文献 17：国际公开第 2008/032064 号小册子

[0036] 专利文献 18：国际公开第 2008/032072 号小册子

[0037] 专利文献 19：国际公开第 2008/032077 号小册子

[0038] 专利文献 20：国际公开第 2008/032086 号小册子

[0039] 专利文献 21：国际公开第 2008/032089 号小册子

[0040] 专利文献 22：国际公开第 2008/032091 号小册子

[0041] 专利文献 23：国际公开第 2007/042810 号小册子

[0042] 专利文献 24：国际公开第 2008/125839 号小册子

[0043] 非专利文献

[0044] 非专利文献 1：「国立癌症研究所杂志 (Journal of the National Cancer Institute)」，2006 年，第 98 卷，545-556 页

[0045] 非专利文献 2：「生物有机化学与药物化学通讯 (Bioorganic & Medicinal Chemistry Letters)」，2006 年，第 16 卷，5973-5977 页

发明内容

[0046] 发明要解决的课题

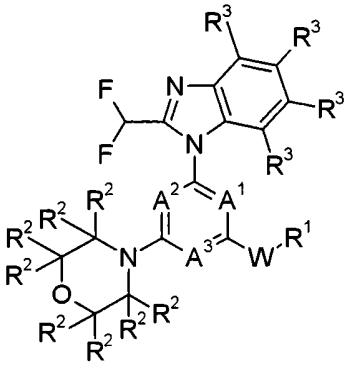
[0047] 本发明的课题是提供一种可用作药物的新型化合物，该化合物可作为各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗剂。

[0048] 解决课题用的手段

[0049] 本发明人对具有 PI3K δ 选择性抑制作用和 / 或 IL-2 产生抑制作用和 / 或 B 细胞增殖抑制作用（包括活化抑制作用）的化合物进行了认真研究，结果发现，一种新型的三嗪或嘧啶衍生物具有优良的 PI3K δ 选择性抑制作用和 / 或 IL-2 产生抑制作用和 / 或 B 细胞增殖抑制作用（包括活化抑制作用），可用作各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗剂，从而完成了本发明。

[0050] 即，本发明涉及式 (I) 的化合物或其盐以及含有式 (I) 的化合物或其盐及赋形剂的药物组合物。

[0051]



(I)

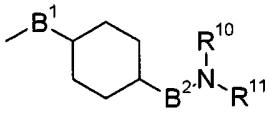
[0052] 式中，

[0053] A^1、A^2 及 A^3：相同或彼此不同，为 CH 或 N，其中 A^1 ～ A^3 中的两个以上为 N；

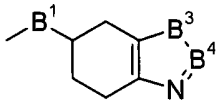
[0054] W：NH 或 O；

[0055] R^1：

[0056]



或



[0057] R^2：相同或彼此不同，为 H 或者可被卤素或 -OH 取代的低级烷基；

[0058] R^3：相同或彼此不同，为 H 或卤素；

[0059] B^1：键或 C_{1-4} 亚烷基；

[0060] B^2：键或 C_{1-4} 亚烷基；

[0061] B^3：O、S 或 NR^0；

[0062] B^4：CR^{12} 或 N；

[0063] R^0：相同或彼此不同，为 H 或低级烷基；

[0064] R^{10}：H；低级烷基，这里的所述低级烷基可被卤素、-C(O)O- 低级烷基、-OH 或 -O- 低

级烷基取代；低级烯基；低级炔基；-低级亚烷基-苯基，这里的所述苯基可被-O-低级烷基取代；-低级亚烷基-O-低级亚烷基-苯基；

[0065] R^{11}：H、R^{100}、-C(O)R^{101}、-C(O)OR^{102}、-C(O)N$R^{103}R^{104}$或-S(O)$_2R^{105}$；

[0066] 或者R^{10}及R^{11}与它们所结合的N一起形成含有1～4个选自O、S和N的杂原子的三～八元的单环杂环基，该单环杂环可被下述基团取代：可被卤素或OH或-O-低级烷基或杂环取代的低级烷基、氧代基、-C(O)O-低级烷基、N(R^0)$_2$、卤素、-CN、-OH、-O-低级烷基、-O-C(O)-低级烷基、-O-低级亚烷基-苯基或杂环基；

[0067] R^{12}：R^0或氨基；

[0068] R^{100}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：卤素、-C(O)N(R^0)$_2$、-C(O)O-低级烷基、-CN、-OH、-O-低级烷基、-O-低级亚烷基-苯基、-NHC(O)O-低级亚烷基-苯基及-S(O)$_2$-低级烷基；低级烯基；低级炔基；

[0069] -X-环烷基，这里的所述环烷基可被选自下述基团的基团取代：低级烷基、苯基、-低级亚烷基-O-低级烷基、-O-低级烷基及-低级亚烷基-苯基，这里的所述苯基可被-O-低级烷基取代；

[0070] -X-芳基，这里的所述芳基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、-CN、-OH、-O-低级烷基、-O-卤代低级烷基、-O-低级亚烷基-OH、-O-低级亚烷基-苯基、-S(O)$_2$-低级烷基、-N(R^0)$_2$、吡咯烷基、可被OH取代的哌啶基、吗啉基及三唑基；或者

[0071] -X-杂环基，这里的所述杂环基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、吗啉基、-C(O)O-低级亚烷基-苯基、-OH、-低级亚烷基-苯基及-低级亚烷基-OH；

[0072] R^{101}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：卤素，-C(O)N(R^0)$_2$，-C(O)-哌嗪基、这里的所述哌嗪基可被-低级亚烷基-OH取代，-CN，-OH，-O-低级烷基，-O-低级亚烷基-苯基，-O-低级亚烷基-O-低级烷基，-O-(可被-CN取代的苯基)，-S(O)$_2$-低级烷基，-S(O)$_2$-苯基，-N(R^0)$_2$，-N(R^0)-低级烷基、这里的所述低级烷基可被-O-低级烷基取代，-NH-苯基，-NHC(O)-低级烷基，-NHC(O)-苯基，-NHC(O)-(可被-OH取代的吡啶基)，-N(R^0)C(O)O-低级烷基，-NHC(O)O-低级亚烷基-苯基，-NHS(O)$_2$-苯基、这里的所述苯基可被选自低级烷基及卤素的基团取代，以及-NHS(O)$_2$-噻吩基；

[0073] -X-环烷基，这里的所述环烷基可被选自下述基团的基团取代：苯基、-CN、-OH、-O-低级烷基及-低级亚烷基-OH；

[0074] -X-苯基，这里的所述苯基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、-C(O)O-低级烷基、-CN、-OH、-O-低级烷基、-N(R^0)$_2$、-N(R^0)-低级亚烷基-OH、-N(-低级亚烷基-OH)$_2$、-NHC(O)-低级烷基、-N(R^0)C(O)N(R^0)$_2$、-S(O)$_2$-低级烷基、-S(O)$_2$N(低级烷基)$_2$、-低级亚烷基-OH、-低级亚烷基-O-低级烷基、-X-哌啶基、-X-吗啉基及-X-(可被低级烷基取代的哌嗪基)；

[0075] -X-杂环基，这里的所述杂环基可被选自下述基团的基团取代：低级烷基、卤素、-OH、卤代低级烷基、苯基、-C(O)O-低级烷基、-C(O)O-低级亚烷基-苯基、-C(O)-(可被-OH取代的吡啶基)、-C(O)-低级烷基、氧代基、-N(R^0)$_2$、-N(R^0)C(O)O-低级烷基、-S(O)$_2$-苯基、可被低级烷基取代的哌啶基、-X-吡啶基、-低级亚烷基-苯基、-低级亚

烷基 -OH、- 低级亚烷基 -O- 低级烷基及 - 低级亚烷基 -（可被低级烷基取代的吡唑基）；或者

[0076] $-C(O)N(R^0)_2$；

[0077] R^{102}：低级烷基；

[0078] R^{103}：H 或低级烷基；

[0079] R^{104}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：-CN、-OH、-O- 低级烷基或 $-N(R^0)_2$；

[0080] -X- 苯基，这里的所述苯基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、-CN、-O- 低级烷基、-O- 卤代低级烷基及 $-N(R^0)_2$；

[0081] -X- 杂环基；

[0082] 或者 R^{103} 及 R^{104} 与它们所结合的 N 一起形成吗啉基；

[0083] R^{105}：低级烷基，这里的所述低级烷基可被选自下述基团的基团取代：卤素、-O- 苯基或杂环基，这里的所述苯基可被 -O- 低级烷基取代；

[0084] 低级烯基；

[0085] -X- 环烷基；

[0086] -X- 芳基，这里的所述芳基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、$-C(O)O-$ 低级烷基、$-C(O)N(R^0)_2$、-CN、-C(O)- 低级烷基、-C(O)- 吡啶基、-O- 低级烷基、-O- 卤代低级烷基、-O- 环烷基、-O- 苯基、-O- 低级亚烷基 -CN、-X-NHC(O)- 低级烷基、-NHC(O)- 吗啉基、$-S(O)_2-$ 低级烷基、$-N(R^0)C(O)N(R^0)_2$、$-S(O)_2N(R^0)_2$ 及 $-S(O)_2-$ 吗啉基；

[0087] -X- 杂环基，这里的所述杂环基可被选自下述基团的基团取代：低级烷基、卤素、卤代低级烷基、苯基、-C(O)- 低级烷基、-C(O)- 卤代低级烷基、-C(O)- 环烷基、-O- 低级烷基、-O- 苯基、氧代基、-NHC(O)- 低级烷基、吗啉基及异噁唑基；或者

[0088] $-N(R^0)_2$；

[0089] X：键或低级亚烷基。

[0090] 本说明书中，如无特别说明，以上所定义的符号采用相同含义。

[0091] 本发明还涉及含有式 (I) 的化合物或其盐的、各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗用药物组合物，即含有式 (I) 的化合物或其盐的、各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防剂或治疗剂。

[0092] 本发明还涉及式 (I) 的化合物或其盐的应用，其用于各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗用药物组合物的制造。

[0093] 本发明还涉及各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗方法，该方法包括给予患者有效量的式 (I) 的化合物或其盐的步骤。

[0094] 本发明还涉及含有式 (I) 的化合物或其盐的 PI3K δ 选择性抑制剂和 / 或 IL-2 产生抑制剂。

[0095] 本发明还涉及各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗用药物组合物的生产方法，该方法包括将式 (I) 的化合物或其盐以及制药学上可接受的载体、溶剂或赋形剂混合的工序。

[0096] 本发明还涉及一种商业包装，该商业包装包括：含有式（I）的化合物或其盐的药物组合物以及式（I）的化合物或其盐可应用于或应当应用于各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗的内容的记载。

[0097] 发明的效果

[0098] 式（I）的化合物由于具有 PI3K δ 选择性抑制作用和 / 或 IL-2 产生抑制作用和 / 或 B 细胞增殖抑制作用（包括活化抑制作用），因此可用作各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗剂。

具体实施方式

[0099] 以下，对本发明进行详细说明。

[0100] 本说明书中的定义中，如无特别说明，“烷基”、“烯基”、“炔基”和“亚烷基”表示直链或支链的烃链。

[0101] “低级烷基”是指碳数 1 ～ 7（以下记作 C_{1-7}）的烷基，作为又一种形态，是指碳数 1 ～ 6（以下记作 C_{1-6}）的烷基，例如有甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、正己基等。作为另一种形态，是指 C_{1-4} 烷基，作为又一种形态，是指甲基、乙基、正丙基、异丙基、叔丁基。

[0102] “低级烯基”是指直链或支链的 C_{2-6} 烯基，例如乙烯基、丙烯基、丁烯基、戊烯基、1- 甲基乙烯基、1- 甲基 -2- 丙烯基、1，1- 二甲基 -2- 丙烯基、1，3- 丁二烯基、1，3- 戊二烯基等。作为另一种形态，是指 C_{2-4} 烯基，作为又一种形态，是指乙烯基、丙烯基、丁烯基、戊烯基、1- 甲基乙烯基、1- 甲基 -2- 丙烯基、1，1- 二甲基 -2- 丙烯基。

[0103] “低级炔基”是指直链或支链的 C_{2-6} 炔基，例如乙炔基、丙炔基、丁炔基、戊炔基、1- 甲基 -2- 丙炔基、1，3- 丁二炔基、1，3- 戊二炔基等。作为另一种形态，是指 C_{2-4} 炔基，作为又一种形态，是指丙炔基、丁炔基、戊炔基、1- 甲基 -2- 丙炔基。

[0104] “低级亚烷基”是指 C_{1-6} 亚烷基，例如亚甲基、1，2- 亚乙基 (ethylene)、1，3- 亚丙基、1，4- 亚丁基、1，5- 亚戊基、1，6- 亚己基、1，2- 亚丙基、甲基亚甲基、乙基亚乙基、1，2- 二甲基亚乙基、1，1，2，2- 四甲基亚乙基等。作为另一种形态，是指 C_{1-5} 亚烷基，作为又一种形态，是指亚甲基、1，2- 亚乙基、1，3- 亚丙基、1，4- 亚丁基、1，5- 亚戊基。

[0105] “卤素”表示 F、Cl、Br、I。

[0106] “卤代低级烷基”是指被 1 个以上的卤素取代了的低级烷基。作为另一种形态，是指被 1 ～ 5 个卤素取代了的低级烷基，作为又一种形态，是指三氟甲基。

[0107] “环烷烃”是指 C_{3-10} 的饱和烃环，可以具有交联。

[0108] “环烷基”是指从环烷烃中除去 1 个氢而得的 C_{3-10} 的饱和烃环基，可以具有交联。例如环丙基、环丁基、环戊基、环己基、环庚基、环辛基、双环 [2.2.1] 庚基、双环 [2.2.2] 辛基、金刚烷基等。作为另一种形态，是指 C_{3-8} 环烷基，作为又一种形态，是指环丙基、环丁基、环戊基、环己基。

[0109] “环烯烃”是指 C_{4-15} 环烯烃。

[0110] “环烯基”是指从环烯烃中除去 1 个氢而得的 C_{4-15} 环烯基。

[0111] “芳基”是指 C_{6-14} 的单环～三环式芳香族烃环基，包括与 C_{5-8} 环烯烃通过其双键部位稠合而成的环基。例如苯基、萘基、四氢萘基、茚满基、茚基、芴基等。作为另一种形态，是

指苯基、萘基、茚满基，作为又一种形态，是指苯基。

[0112] “杂环”基是指选自下组的环基：i）含有 1 ～ 4 个选自 O、S 及 N 的杂原子的三～八元的单环杂环，作为另一种形态，是五～七元的单环杂环；ii）由所述单环杂环与选自单环杂环、苯环、C_{5-8} 环烷烃及 C_{5-8} 环烯烃的 1 个或 2 个环稠合而形成的含有 1 ～ 5 个选自 O、S 及 N 的杂原子的双环～三环式杂环。作为成环原子的 S 或 N 可以被氧化而形成氧化物或二氧化物，可以具有交联，可以形成螺环。

[0113] 作为“杂环”基，可例举例如氮杂环丙烷基、氮杂环丁烷基、吡咯烷基、哌啶基、氮杂环庚烷基、氮杂环辛烷基、哌嗪基、高哌嗪基、环氧乙烷基、氧杂环丁烷基、四氢呋喃基、四氢吡喃基、四氢噻吩基、四氢噻喃基、吗啉基、高吗啉基、异噻唑烷基、硫代吗啉基、吡咯基、吲哚基、咪唑基、吡唑基、吡啶基、嘧啶基、吡嗪基、三唑基、四唑基、呋喃基、噻吩基、噁唑基、异噁唑基、噁二唑基、噻唑基、噻二唑基、二氢苯并噻吩基、苯并咪唑基、四氢苯并咪唑基、二氢苯并噁唑基、苯并异噁唑基、喹啉基、四氢喹啉基、四氢异喹啉基、喹唑啉基、喹喔啉基、苯并呋喃基、苯并噻吩基、苯并噁唑基、苯并噻唑基、二氢苯并噻唑基、四氢苯并噻唑基、咔唑基、吲哚基、二氢吲哚基、四氢喹啉基、四氢异喹啉基、奎宁环基、二苯并呋喃基、二苯并呋喃基、1,3- 苯并间二氧杂环戊烯 -5- 基、色满基、二氢苯并噁嗪基、1,4- 苯并二喔星基（ベンゾジオキシニル基）。作为另一种形态，是指五～十元的单环～双环式杂环基。作为又一种形态，是指氮杂环丁烷基、吡咯烷基、哌啶基、氮杂环庚烷基、氮杂环辛烷基、哌嗪基、四氢呋喃基、四氢吡喃基、四氢噻吩基、四氢噻喃基、吗啉基、高吗啉基、异噻唑烷基、硫代吗啉基、咪唑基、吡唑基、吡啶基、嘧啶基、吡嗪基、三唑基、四唑基、呋喃基、噻吩基、噁唑基、异噁唑基、噻唑基、噻二唑基、吲哚基、二氢吲哚基、二氢苯并噻吩基、苯并咪唑基、四氢苯并咪唑基、二氢苯并噁唑基、苯并异噁唑基、苯并噻唑基、二氢苯并噻唑基、四氢苯并噻唑基、喹啉基、四氢喹啉基、四氢异喹啉基、色满基、二氢苯并噁嗪基、1,4- 苯并二喔星基。

[0114] “饱和杂环”基是指所述“杂环”基中构成环的键只有单键的基团。

[0115] 作为“饱和杂环”基，可例举例如氮杂环丁烷基、吡咯烷基、哌啶基、氮杂环庚烷基、氮杂环辛烷基（アゾカニル）、哌嗪基、四氢呋喃基、四氢吡喃基、四氢噻吩基、四氢噻喃基、吗啉基、异噻唑烷基、硫代吗啉基。

[0116] 本说明书中，“可被取代”是指非取代或具有 1 ～ 5 个取代基。具有多个取代基时，这些取代基既可以相同也可以彼此不同。

[0117] “PI3K δ 选择性抑制剂”是指显示出如下数值的抑制剂：以 IC_{50} 值计，PI3K α 的抑制活性相对于 PI3K δ 的抑制活性为 10 倍以上，作为另一种形态为 30 倍以上，作为又一种形态为 100 倍以上。

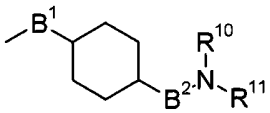
[0118] 下面示出本发明的式 (I) 的化合物的某些形态。

[0119] (1)A^3 为 N 的化合物；作为另一种形态，是 A^1、A^2 及 A^3 为 N 的化合物；作为又一种形态，是 A^1 为 CH 且 A^2 及 A^3 为 N、或者 A^2 为 CH 且 A^1 及 A^3 为 N 的化合物；作为又一种形态，是 A^1 为 CH 且 A^2 及 A^3 为 N 的化合物；作为又一种形态，是 A^2 为 CH 且 A^1 及 A^3 为 N 的化合物。

[0120] (2)W 为 NH 的化合物；作为另一种形态，是 W 为 O 的化合物。

[0121] (3)R^1 为

[0122]



[0123] 的化合物。

[0124] (4)R^2 相同或彼此不同，为 H 或者可被卤素或 -OH 取代的低级烷基的化合物；作为另一种形态，R^2 相同或彼此不同，为 H 或低级烷基；作为又一种形态，是 R^2 为 H 的化合物；作为又一种形态，是 R^2 为低级烷基的化合物；作为又一种形态，是 R^2 为可被卤素或 -OH 取代的低级烷基的化合物。

[0125] (5)R^3 为 H 的化合物。

[0126] (6)B^1 为键的化合物；作为另一种形态，是 B^1 为 C_{1-4} 亚烷基的化合物；作为又一种形态，是 B^1 为亚甲基的化合物；作为又一种形态，是 B^1 为键或亚甲基的化合物。

[0127] (7)B^2 为键的化合物；作为另一种形态，是 B^2 为 C_{1-4} 亚烷基的化合物；作为又一种形态，是 B^2 为亚甲基的化合物；作为又一种形态，是 B^2 为键或亚甲基的化合物。

[0128] (8)R^{10} 为 H、可被卤素或 -OH 取代的低级烷基、- 低级亚烷基 -O- 低级烷基、低级烯基、低级炔基、- 低级亚烷基 - 苯基或 - 低级亚烷基 -O- 低级亚烷基 - 苯基的化合物，这里的所述苯基可被 -O- 低级烷基取代；作为另一种形态，是 R^{10} 为 H、低级烷基、或 - 低级亚烷基 -O- 低级烷基的化合物；作为又一种形态，是 R^{10} 为 H 的化合物；作为有一种形态，是 R^{10} 为低级烷基的化合物；作为又一种形态，是 R^{10} 为 - 低级亚烷基 -O- 低级烷基的化合物。

[0129] (9)R^{11} 为 R^{100} 或 $-C(O)R^{101}$ 的化合物；作为另一种形态，是 R^{11} 为 R^{100} 的化合物；作为又一种形态，是 R^{11} 为 $-C(O)R^{101}$ 的化合物；作为又一种形态，是 R^{11} 为 $-C(O)OR^{102}$ 的化合物；作为又一种形态，是 R^{11} 为 $-C(O)NR^{103}R^{104}$ 的化合物；作为又一种形态，是 R^{11} 为 $-S(O)_2R^{105}$ 的化合物。

[0130] (10)R^{10} 及 R^{11} 与它们所结合的 N 一起形成含有 1 ～ 4 个选自 O、S 和 N 的杂原子的三～八元的单环杂环基的化合物，该单环杂环可被低级烷基、氧代基、卤代低级烷基、- 低级亚烷基 -OH、-C(O)O- 低级烷基、$-C(O)NR^{103}R^{104}$、$N(R^0)_2$、卤素、-CN、-OH、-O- 低级烷基、- 低级亚烷基 -O- 低级烷基或杂环基取代；作为另一种形态，是 R^{10} 及 R^{11} 与它们所结合的 N 一起形成含有 1 ～ 4 个选自 O、S 和 N 的杂原子的三～八元的单环杂环基的化合物，该单环杂环为低级烷基或氧代基。

[0131] (11)R^{100} 为可被选自 -OH、卤素及 -O- 低级烷基的基团取代的低级烷基的化合物；作为另一种形态，是 R^{100} 为可被选自卤素及 -O- 低级烷基的基团取代的低级烷基的化合物。

[0132] (12)R^{101} 为可被选自卤素、-OH、-O- 低级烷基及 $-N(R^0)_2$ 的基团取代的低级烷基的化合物。

[0133] (13) 上述 (1) ～ (12) 中记载的基团中的两种以上的组合的化合物或其制药学上可接受的盐。

[0134] 作为上述 (13) 的化合物的具体示例，可例举以下化合物。

[0135] (14)(3) 中记载的化合物，其中 A^1 为 CH 且 A^2 及 A^3 为 N、或者 A^2 为 CH 且 A^1 及 A^3 为 N。

[0136] (15)(14) 中记载的化合物，其中 B^1 为键或亚甲基且 B^2 为键。

[0137] (16)(15) 中记载的化合物，其中 R^2 相同或彼此不同，为 H 或低级烷基。

[0138] (17)(16) 中记载的化合物，其中 R^3 为 H。

[0139] (18)(17) 中记载的化合物，其中 R^{10} 为 H、可被卤素或 -OH 取代的低级烷基、- 低级亚烷基 -O- 低级烷基、低级烯基、低级炔基、- 低级亚烷基 - 苯基或 - 低级亚烷基 -O- 低级亚烷基 - 苯基，这里的所述苯基可被 -O- 低级烷基取代。

[0140] (19)(17) 中记载的化合物，其中 R^{10} 为 H、低级烷基或 - 低级亚烷基 -O- 低级烷基。

[0141] (20)(18) 或 (19) 中记载的化合物，其中 R^{11} 为 R^{100} 或 $-C(O)R^{101}$。

[0142] (21)(20) 中记载的化合物，其中 R^{100} 为可被选自 -OH、卤素及 -O- 低级烷基的基团取代的低级烷基。

[0143] (22)(20) 中记载的化合物，其中 R^{100} 为可被选自卤素及 -O- 低级烷基的基团取代的低级烷基。

[0144] (23)(20) 中记载的化合物，其中 R^{101} 为可被选自卤素、-OH、-O- 低级烷基及 $-N(R^0)_2$ 的基团取代的低级烷基。

[0145] (24)(17) 中记载的化合物，其中 R^{10} 及 R^{11} 与它们所结合的 N 一起形成含有 1 ～ 4 个选自 O、S 和 N 的杂原子的三～八元的单环杂环基，该单环杂环可被选自低级烷基、氧代基、卤代低级烷基、- 低级亚烷基 -OH、-C(O)O- 低级烷基、$-C(O)NR^{103}R^{104}$、$N(R^0)_2$、卤素、-CN、-OH、-O- 低级烷基、- 低级亚烷基 -O- 低级烷基或杂环基取代。

[0146] (25)(17) 中记载的化合物，其中 R^{10} 及 R^{11} 与它们所结合的 N 一起形成含有 1 ～ 4 个选自 O、S 和 N 的杂原子的三～八元的单环杂环基，该单环杂环可被低级烷基或氧代基取代。

[0147] (26) 选自下组的式 (I) 记载的化合物或其制药学上可接受的盐：

[0148] N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氧基) 环己基]-N,N- 二甲基甘氨酰胺、

[0149] N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基]-N,N- 二甲基甘氨酰胺、

[0150] 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-({ 反 -4-[(2- 氟乙基)(甲基) 氨基] 环己基 } 甲基)-6- 吗啉 -4- 基嘧啶 -2- 胺、

[0151] 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-({ 反 -4-[(2- 甲氧基乙基)(甲基) 氨基] 环己基 } 甲基)-6- 吗啉 -4- 基嘧啶 -2- 胺、

[0152] 6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基 -N-[(反 -4- 吗啉 -4- 基环己基) 甲基] 嘧啶 -4- 胺、

[0153] 1-[{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-[(3S)-3- 甲基吗啉 -4- 基] 嘧啶 -2- 基 } 氨基) 甲基] 环己基 }(甲基) 氨基]-2- 甲基丙烷 -2- 醇、

[0154] 1-[{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-[(3S)-3- 甲基吗啉 -4- 基] 嘧啶 -2- 基 } 氨基) 甲基] 环己基 }(乙基) 氨基]-2- 甲基丙烷 -2- 醇、

[0155] 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-({ 反 -4-[乙基 (1- 甲氧基丙烷 -2- 基) 氨基] 环己基 } 甲基)-6-(吗啉 -4- 基) 嘧啶 -2- 胺、

[0156] 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-{[反 -4-(二丙基氨基) 环己基] 甲基 }-6-(吗啉 -4- 基) 嘧啶 -2- 胺、

[0157] 3-[{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 }(甲基) 氨基]-2- 甲基丁烷 -2- 醇、

[0158] 6-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(3S)-3-氟吡咯烷-1-基]环己基}甲基)-2-(吗啉-4-基)嘧啶-4-胺、

[0159] 3-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3S)-3-甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}(甲基)氨基]-2-甲基丁烷-2-醇、

[0160] 3-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}(甲基)氨基]-2-甲基丁烷-2-醇、

[0161] 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(1-甲氧基丙烷-2-基)(甲基)氨基]环己基}甲基)-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-胺、

[0162] 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[乙基(1-甲氧基丙烷-2-基)氨基]环己基}甲基)-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-胺、

[0163] 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2S)-2-(氟甲基)吡咯烷-1-基]环己基}甲基)-6-(吗啉-4-基)嘧啶-2-胺、及

[0164] 6-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2S)-2-(氟甲基)氮杂环丁烷-1-基]环己基}甲基)-2-(吗啉-4-基)嘧啶-4-胺。

[0165] 根据取代基的种类,式(I)的化合物可存在互变异构体或几何异构体。本说明书中,式(I)的化合物只记载了异构体的一种形态,但本发明还包括除此之外的异构体,还包括分离开的异构体或它们的混合物。

[0166] 此外,式(I)的化合物有时具有不对称碳原子或手性轴(轴不齐),可存在基于该不对称碳原子或手性轴的光学异构体。本发明还包括式(I)的化合物的分离开的光学异构体或它们的混合物。

[0167] 本发明还包括式(I)的化合物的制药学上可接受的前药。制药学上可接受的前药是指具有通过溶剂分解或在生理条件下可转化成氨基、羟基、羧基等的基团的化合物。作为形成前药的基团,可例举例如 Prog. Med.,5,pp.2157-2161(1985)和“医药品的开发”(广川书店,1990 年)第 7 卷 分子设计 pp.163-198 中记载的基团。

[0168] 式(I)的化合物根据取代基的种类的不同有时会形成酸加合盐或形成与碱的盐,只要该盐是制药学上可接受的盐,即包含在本发明中。具体可例举:与盐酸、氢溴酸、氢碘酸、硫酸、硝酸、磷酸等无机酸的酸加成盐;或者,与甲酸、乙酸、丙酸、草酸、丙二酸、琥珀酸、富马酸、马来酸、乳酸、苹果酸、扁桃酸、酒石酸、二苯甲酰酒石酸、二甲苯酰酒石酸、柠檬酸、甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、天冬氨酸、谷氨酸等有机酸的酸加成盐;与钠、钾、镁、钙、铝等无机碱所成的盐;或者,与甲胺、乙胺、乙醇胺、赖氨酸、鸟氨酸等有机碱所成的盐;与乙酰基亮氨酸等各种氨基酸及氨基酸衍生物所成的盐或铵盐等。

[0169] 本发明还包括式(I)的化合物及其制药学上可接受的盐的各种水合物和溶剂合物以及多晶形物质。此外,本发明也包括用各种放射性或非放射性同位素标记的化合物。

[0170] (制造方法)

[0171] 式(I)的化合物及其制药学上可接受的盐可利用基于其基本骨架或取代基种类的特征,采用各种公知的合成法来制造。此时,根据官能团的种类,在从原料到中间体的阶段将该官能团置换成合适的保护基(能容易地转化成该官能团的基团)的方法有时在制造技术上很有效。作为这样的官能团,例如有氨基、羟基、羧基等,作为它们的保护基,可例举例如格林(Greene)及伍兹(Wuts)著、“有机合成中的保护基(Protective Groups in

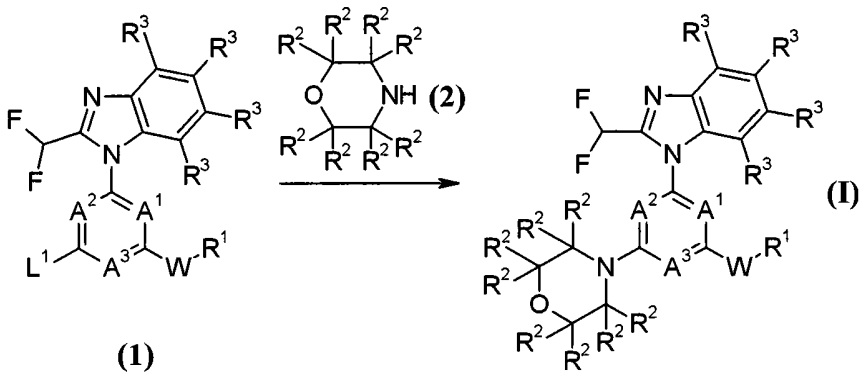
Organic Synthesis)(第 3 版,1999 年)”中记载的保护基等,可以根据它们的反应条件适当选择使用。上述方法中,在导入该保护基并进行了反应后,可根据需要通过除去保护基而得到所要的化合物。

[0172] 此外,式 (I) 的化合物的前药可以与上述保护基同样地通过在从原料到中间体的阶段导入特定基团的方法或使用所得的式 (I) 的化合物进一步进行反应来制造。反应通常可采用酯化、酰胺化、脱水等本领域技术人员所公知的方法来进行。

[0173] 下面对式 (I) 的化合物的代表性的制造方法进行说明。各制法也可参照该说明中所附的参考文献来进行。应予说明,本发明的制造方法不局限于以下所示的例子。

[0174] (第一制法)

[0175]



[0176] (式中,L^1 表示离去基团。以下同样)

[0177] 式 (I) 的化合物可通过化合物 (1) 与化合物 (2) 的反应获得。离去基团的离子包括卤素、甲基亚硫酰基或甲基磺酰基。

[0178] 该反应中,使用等量或一方过量的化合物 (1) 和化合物 (2),将它们的混合物在对反应呈惰性的溶剂中或在无溶剂的条件下,在冷却～加热回流下、较好是 0℃～ 100℃下搅拌,通常历时 0.1 小时～ 5 天。这里所用的溶剂的例子没有特别限制,可例举苯、甲苯、二甲苯等芳香族烃类,乙醚、四氢呋喃、二噁烷、二甲氧基乙烷等醚类,二氯甲烷、1,2- 二氯乙烷、氯仿等卤代烃类,N,N- 二甲基甲酰胺、N,N- 二甲基乙酰胺、二甲亚砜、乙酸乙酯、乙腈及它们的混合物。在三乙胺、N,N- 二异丙基乙胺或 N- 甲基吗啉等有机碱或者碳酸钾、碳酸钠、碳酸铯或氢氧化钾等无机碱的存在下进行反应有时有利于使反应顺畅地进行。

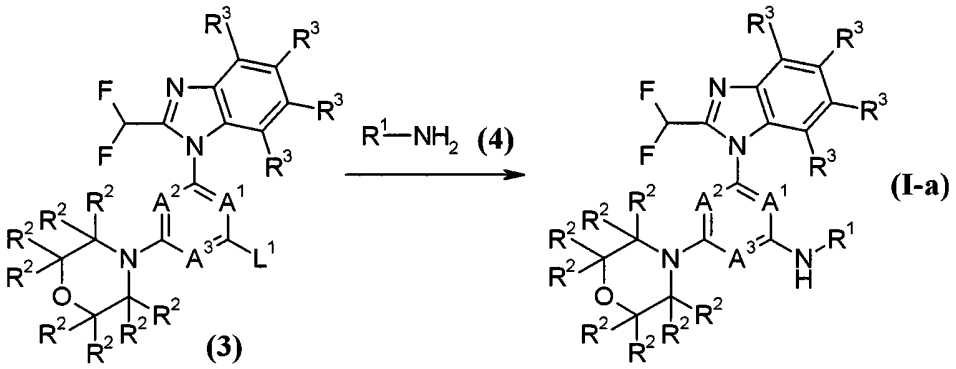
[0179] 〔文献〕

[0180] S.R.Sandler 及 W.Karo 著,“有机官能团制备”,第 2 版,第 1 卷,Academic Press Inc.,1991 年

[0181] 日本化学会编“第 5 版实验化学讲座(第 14 卷)”,丸善,2005 年

[0182] (第二制法)

[0183]



[0184] 式 (I-a) 的化合物可通过化合物 (3) 与化合物 (4) 的反应获得。反应条件同第一制法。

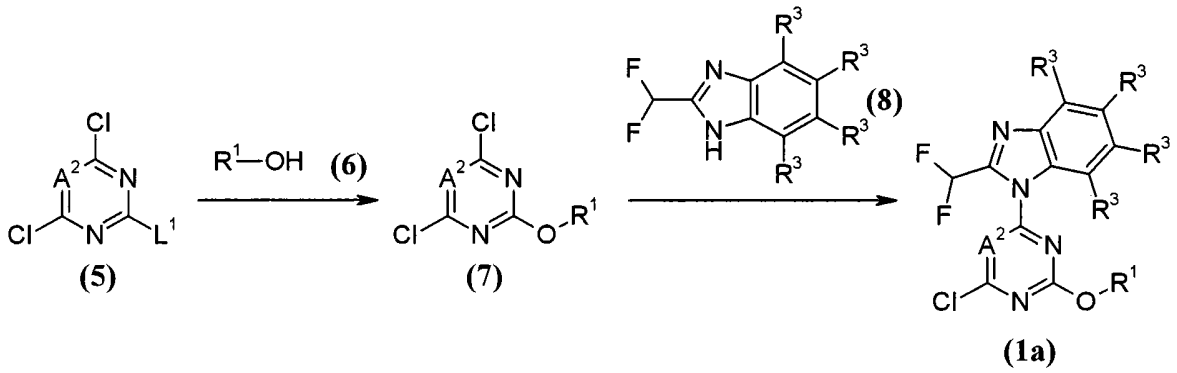
[0185] 式 (I) 的化合物中的基团 R^1 及 R^2 上的各种取代基能够以式 (I) 的化合物为原料，通过采用后述实施例中记载的反应、对本领域技术人员而言显而易见的反应或它们的变通方法来容易地转化成其它官能团。例如，可任意地组合实施 O- 烷基化、N- 烷基化、还原、水解、酰胺化等本领域技术人员通常采用的工序。

[0186] （原料化合物的制造）

[0187] 上述制造方法中的原料化合物可采用例如下述方法、下述实施例中记载的方法、公知的方法或它们的变通方法来制造。

[0188] （原料合成 1）

[0189]

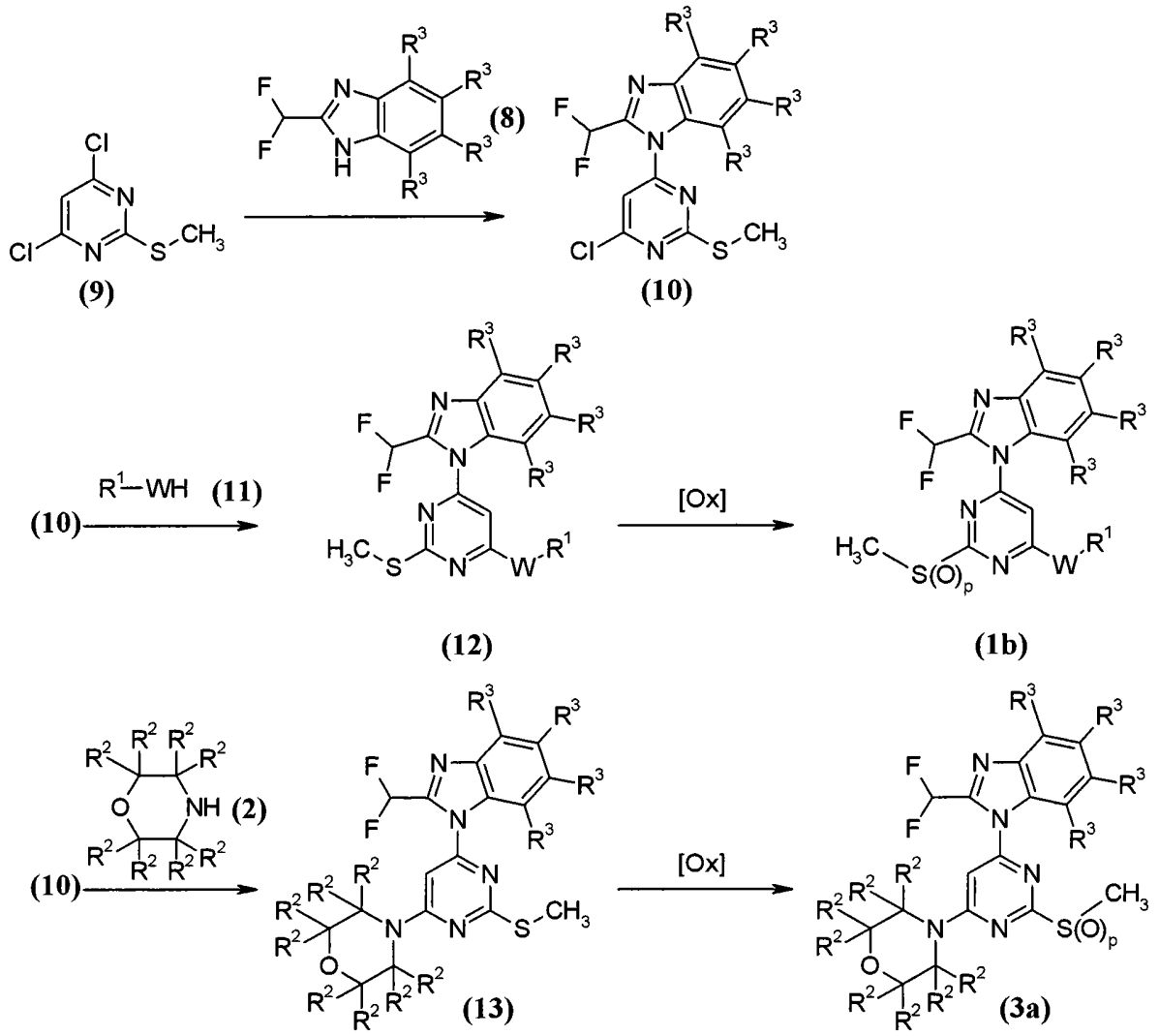


[0190] 化合物 (7) 可通过化合物 (5) 与化合物 (6) 的反应获得。该反应中，使用等量或一方过量的化合物 (5) 和化合物 (6)，在碱的存在下将它们的混合物在对反应呈惰性的溶剂中或在无溶剂的条件下，在冷却～加热回流下搅拌，通常历时 0.1 小时～ 5 天。这里所用的溶剂的例子没有特别限制，可例举苯、甲苯、二甲苯等芳香族烃类，乙醚、四氢呋喃、二噁烷、二甲氧基乙烷等醚类，二氯甲烷、1，2- 二氯乙烷、氯仿等卤代烃类，N，N- 二甲基甲酰胺、N，N- 二甲基乙酰胺、二甲亚砜、乙酸乙酯、乙腈及它们的混合物。作为碱的例子，可例举三乙胺、N，N- 二异丙基乙胺或 N- 甲基吗啉等有机碱或者碳酸钾、碳酸钠、碳酸铯、碳酸氢钠、氢氧化钾或氢化钠等无机碱。添加冠醚等有时有利于使反应顺畅地进行。。

[0191] 化合物 (1a) 可通过使化合物 (7) 与化合物 (8) 在碱的存在下反应而获得。

[0192] （原料合成 2）

[0193]



[0194] （式中，Ox 表示氧化剂，p 表示 1 或 2。以下同样）

[0195] 化合物 (10) 可通过使化合物 (9) 与化合物 (8) 在碱的存在下反应而获得。

[0196] 化合物 (12) 可通过使化合物 (10) 与化合物 (11) 在碱的存在下反应而获得。通过微波照射对反应混合物加热有时有利于使反应顺畅地进行。

[0197] 化合物 (1b) 可通过化合物 (12) 的氧化反应获得。氧化反应可使用等量或一方略微过量的化合物 (12) 和间氯过苯甲酸、过乙酸、过氧化氢水等氧化剂，在冷却～加热下进行。作为溶剂，可单独使用芳香族烃类、卤代烃类等溶剂，或者 2 种以上混合使用。

[0198] 也可在与上述同样的反应条件下通过化合物 (10) 与化合物 (2) 的反应而获得化合物 (13)，接着再获得化合物 (3a)。

[0199] 其它原料化合物 (3) 可参考例如以下文献中记载的方法来制造。WO2002/088112、EP1389617、WO2008/032033、WO2008/032036、WO2008/032041 或 WO2008/032060。

[0200] 式 (I) 的化合物能以游离化合物、其制药学上可接受的盐、水合物、溶剂合物或多晶形物质的形式分离、纯化。式 (I) 的化合物的制药学上可接受的盐也可通过进行常规的成盐反应来制造。

[0201] 分离、纯化采用萃取、分级结晶、各种分级（分画）色谱法等常规的化学操作来进行。

[0202] 各种异构体可通过选择合适的原料化合物来制造，或者利用异构体之间的物理化学性质的差异来分离。例如，对于光学异构体，可通过外消旋体的常规的光学拆分法（例如转化为与具有光学活性的碱或酸的非对映异构体盐的分级结晶、使用手性柱等的色谱法等）而获得，或者也可由合适的光学活性原料化合物来制造。

[0203] 式（I）的化合物的药理活性通过以下试验确认。

[0204] 1.PI3Kδ 酶抑制活性

[0205] 实验中使用 PI3- 激酶 HTRF 试验试剂盒（PI3-Kinase HTRF Assay kit）（Millipore 公司，目录号 33-016）和人 PI3Kδ 酶（Millipore 社，目录号 14-604）。测定方法按照附带的说明书。下面示出其简要内容。

[0206] 将 PI3Kδ（10ng/ 孔）、磷脂酰肌醇 -4,5- 二磷酸（10μM）、ATP（30μM）及试验化合物在 384 孔板中混合（总量 20μL），室温下培养 30 分钟。添加 EDTA 及生物素化磷脂酰肌醇 -3,4,5- 三磷酸，使反应停止。然后添加铕标记抗 GST 抗体、GST 结合 GRP1PH 域及链霉抗生物素 -APC，培养过夜。用 HTRF 平板读取器测定 HTRF 比。将未添加酶时的抑制率设为 100%，将添加酶而未添加试验化合物时的抑制率设为 0%，通过 logistic 法算出化合物的 IC_{50} 值。

[0207] 2.PI3Kα 酶抑制活性

[0208] 将人 PI3Kα（12ng/ 孔，Millipore 公司，目录号 14-602）、磷脂酰肌醇（0.2μg/ 孔）及试验化合物在反应缓冲液（50mM Hepes、10mM NaCl、10mM $MgCl_2$、2mM EGTA、2mM DTT、pH 7.3）中在 384 孔板中混合（总量 10μL），于 37℃培养 3 小时。反应后，添加 10μL 的 Kinase-Glo Plus 试剂（Promega 公司，目录号 V3772），用发光计测定发光。将未添加酶时的抑制率设为 100%，将未添加试验化合物时的抑制率设为 0%，通过 logistic 法算出化合物的 IC_{50} 值。

[0209] 各化合物的结果示于表 1 和表 2。表中，Ex 表示下述实施例的化合物编号，PI3Kδ 表示 PI3Kδ 酶抑制活性的 IC_{50} 值（nM），PI3Kα 表示 PI3Kα 酶抑制活性的 IC_{50} 值（nM）。

[0210] [表 1]

[0211]

Ex	PI3K δ	PI3K α
4	33	2000
5	11	210
6	4.6	330
10	7.1	1500
11	14	930
14	4.4	1400
18	5.0	2900
24	5.2	>3000
27	20	990
39	9.5	470
40	3.6	1200
46	44	>3000
47	16	900
52	3.4	2700
53	4.6	2700
95	4.9	2500
104	2.1	810
107	8.8	3000
108	2.8	2200
112	4.6	1400
116	5.2	180
123	0.85	460
125	1.8	>3000
154	3.8	1800
174	5.9	2400
177	4.8	>3000
185	4.3	>3000
187	9.1	3000
190	4.1	>3000
193	23	550
206	4.4	3300
208	8.6	2300
209	20	2800

Ex	PI3K δ	PI3K α
210	22	5100
216	5.6	>3000
219	14	6000
223	6.2	>10000
229	10	6700
231	8.2	1500
246	5.5	1700
271	2.6	2500
274	9.7	>3000
280	4.9	2500
330	8.6	5500
344	14	1000
363	18	1400
374	6.4	1200
375	12	1600
384	16	1600
385	21	3000
393	7.7	780
396	13	2300
397	23	2900
398	32	3400
399	22	3200
401	15	3500
402	3.6	610
403	4.9	700
422	6.0	5800
423	11	4200
424	6.0	3600
430	2.3	2300

[0212] [表 2]

[0213]

Ex	PI3K δ	PI3K α
434	4.3	1900
435	2.8	950
437	7.1	2200
438	3.6	2400
441	15	5900
442	10	2700
445	7.0	3400
446	8.9	1700
447	5.3	2900
449	14	1300
450	14	3500
456	13	1800
461	16	3800
471	8.1	1700
473	30	9900
481	8.9	1100
482	4.6	3400
483	15	8700
484	1.5	2600
485	31	>10000
486	9.8	3600
487	7.9	4400

Ex	PI3K δ	PI3K α
488	30	5600
490	9.4	1600
491	4.5	570
495	14	6700
496	17	7600
497	16	10000
499	11	1500
500	14	>10000
505	4.1	450
506	4.3	590
507	4.9	490
508	4.6	620
510	36	>10000
511	4.7	2000
512	23	>10000
513	3.5	3100
515	6.0	1200
527	14	5700
539	7.6	2200
546	50	5500

[0214] 3. 大鼠体内 IL-2 产生抑制试验

[0215] 实验中使用雄性 LEW/CrlCrlj 大鼠（日本查尔斯河）(6 周龄，体重 130-180g)。将试验化合物悬浮于 0.5％甲基纤维素溶液，以 5mL/kg 口服给药。以 15mg/kg 的用量尾静脉注射伴刀豆球蛋白 A（船越株式会社，目录号 L-1000)，藉此诱发 IL-2 产生。

[0216] 试验按照以下所示的试验方案进行。给予伴刀豆球蛋白 A 之前 2 小时或 16 小时，口服给予大鼠试验化合物。给予伴刀豆球蛋白 A，3 小时后进行采血。用 ELISA 试剂盒 (R&D Systems，Inc.，目录号 DY502E) 定量血中的 IL-2 浓度。根据试验化合物给药组的 IL-2 产生量相对于给予载体的对照组的 IL-2 产生量的值算出抑制率。

[0217] 其结果是，确认式 (I) 的化合物具有优良的 IL-2 产生抑制活性。例如，在给予伴刀豆球蛋白 A 两小时之前给予试验化合物 (10mg/kg) 的情况下，实施例 4、11、24、40、46、194、201、202、206 及 219 的化合物分别显示出 83％、80％、79％、94％、71％、89％、76％、80％、83％及 78％的抑制活性。

[0218] 4. 大鼠 B 细胞增殖抑制试验

[0219] 使用含 10％ FCS 的 RPMI-1640 培养基，将由雄性 LEW/CrlCrlj 大鼠（日本查尔

斯河）制备的脾细胞（1.0x 10^5 个细胞／孔）、小鼠 F(ab')$_2$ 片段抗－大鼠 IgM(3μg/孔，SouthernBiotech 公司，目录号 3082-14)、及溶解于 DMSO 的试验化合物（最终 DMSO 浓度 0.1%）在 96 孔板中混合（总量 200μL)。在 CO_2 培养箱内培养 48 小时，培养结束 4 小时前以 0.037MBq/孔的量添加 [^{3}H] 胸苷 (925GBq/mmol，Moravek Biochemicals 公司，目录号 MT6038)。用细胞收集器将细胞回收至 GF/C 玻璃滤器，用液体闪烁计数器测定滤器上的放射能量。将未添加 IgM 时的 dpm（每分钟衰变）设为抑制率 100%，将未添加试验化合物时的 dpm 设为抑制率 0%，通过 logistic 法算出化合物的 IC_{50} 值。

[0220] 各化合物的结果示于表 3。表中，Ex 表示下述实施例的化合物编号，IC_{50} 值 (nM) 表示 B 细胞增殖抑制活性。

[0221] [表 3]

[0222]

Ex	IC_{50}(nM)
4	1.8
11	6.1
24	4.2
40	0.62
46	5.2
174	2.4
177	1.1
206	4.1
219	3.5
223	1.5
246	2.1
271	5.5
274	5.5
280	3.8
363	1.4
374	2.0
375	1.2
385	1.9
393	0.70
398	2.3
399	3.4
403	0.82

Ex	IC_{50}(nM)
422	4.9
424	1.7
430	1.8
434	1.3
435	0.58
437	3.6
438	3.0
441	4.2
442	1.2
445	0.72
446	1.7
447	0.77
449	2.2
450	2.1
456	1.1
461	1.1
471	1.3
473	4.0
482	4.6
484	2.2
486	3.6
487	1.4

Ex	IC_{50}(nM)
488	2.8
490	0.76
491	1.8
495	1.7
496	1.7
497	2.1
500	2.7
505	0.46
506	0.75
507	0.38
508	0.37
510	18
511	1.2
512	10
513	0.64
515	4.1
527	2.8
539	0.84
546	2.2

[0223] 由上述试验的结果可以确认，式 (I) 的化合物具有优良的 PI3Kδ 选择性抑制作用和／或 IL-2 产生抑制作用和／或 B 细胞增殖抑制作用（包括活化抑制作用）。因此可用作各种脏器移植中的排斥反应、变应性疾病、自身免疫疾病和血液肿瘤等的预防或治疗剂。

[0224] 上述各种脏器移植是指例如肾脏、肝脏、心脏等的移植。上述排斥反应包括与 T 细胞相关的 T 细胞关联型排斥反应、与 B 细胞相关的抗体关联型排斥反应。上述变应性疾病是指哮喘、特应性皮炎等。上述自身免疫疾病是指类风湿性关节炎、牛皮癣、溃疡性结肠炎、克罗恩病、全身性红斑狼疮等。血液肿瘤是指白血病等。

[0225] 因为式 (I) 的化合物是 PI3Kδ 抑制作用远远强于 PI3Kα 抑制作用的选择性抑制剂，所以可成为不会引发基于 PI3Kα 抑制作用的胰岛素抵抗的优秀的免疫抑制剂。

[0226] 含有式 (I) 的化合物或其盐中的 1 种或 2 种以上作为有效成分的药物组合物可使用本领域内常用的赋形剂、即药剂用赋形剂或药剂用载体等通过常用的方法来制备。

[0227] 给药可以是采用片剂、丸剂、胶囊剂、颗粒剂、散剂、液体制剂等口服给药或采用关节内、静脉内、肌肉内等的注射剂、栓剂、滴眼剂、眼软膏、透皮用液体制剂、软膏剂、透皮用贴剂、经粘膜液体制剂、经粘膜贴剂、吸入剂等的胃肠外给药中的任一种形态。

[0228] 作为口服给药用的固体组合物，可使用片剂、散剂、颗粒剂等。该固体组合物中，将 1 种或 2 种以上的有效成分与例如乳糖、甘露糖醇、葡萄糖、羟丙基纤维素、微晶纤维素、淀粉、聚乙烯吡咯烷酮和 / 或偏硅酸铝镁等至少 1 种惰性赋形剂混合。组合物根据常规方法可含有惰性添加剂，例如硬脂酸镁之类的润滑剂、羧甲基淀粉钠等之类的崩解剂、稳定剂、助溶剂。片剂或丸剂根据需要可用糖衣或者胃溶性或肠溶性物质的膜包衣。

[0229] 口服给药用的液体组合物包含药剂学上可接受的乳剂、溶液剂、混悬剂、糖浆剂或酏剂等，包含常用的惰性稀释剂，例如精制水或乙醇。该液体组合物除包含惰性稀释剂以外，也可包含增溶剂、湿润剂、混悬剂之类的助剂、甜味剂、矫味剂、芳香剂、防腐剂。

[0230] 胃肠外给药用的注射剂包含无菌的水性或非水性的溶剂、混悬剂或乳剂。作为水性的溶剂，例如包括注射用蒸馏水或生理盐水。作为非水性的溶剂，例如有丙二醇、聚乙二醇、橄榄油之类的植物油、乙醇之类的醇类、或聚山梨醇酯 80（药典名）等。上述组合物还可包含等渗剂、防腐剂、湿润剂、乳化剂、分散剂、稳定剂或助溶剂。它们可藉由例如使它们通过保留细菌的滤器的过滤、杀菌剂的配合或照射来实现无菌化。此外，它们也可以制成无菌的固体组合物，在使用前溶解或悬浮于无菌水或无菌的注射用溶剂中来使用。

[0231] 作为外用剂，包括软膏剂、硬膏剂、霜剂、胶冻剂、巴布剂、喷雾剂、洗剂、滴眼剂、眼软膏等。可包含常用的软膏基剂、洗剂基剂、水性或非水性的液体制剂、混悬剂、乳剂等。例如，作为软膏或洗剂基剂，可例举聚乙二醇、丙二醇、白凡士林、白蜂蜡、聚氧乙烯硬化蓖麻油、单硬脂酸甘油酯、十八醇、十六醇、聚桂醇、失水山梨糖醇倍半油酸酯等。

[0232] 吸入剂或经鼻剂等经粘膜剂采用固体、液体或半固体状的剂型，可通过现有公知的方法制造。例如可适当添加公知的赋形剂，还可适当添加 pH 调整剂、防腐剂、表面活性剂、润滑剂、稳定剂、增稠剂等。给药可使用合适的吸入或吹送用装置。例如，可以使用计量给药吸入装置等公知的装置或喷雾器，将化合物单独制成粉末或按照配方制成混合物的粉末来给药，或者与药学上可接受的载体组合制成溶液或悬浮液来给药。既可以使用干燥粉末吸入器等单次或多次给药用的装置，也可以使用干燥粉末或含粉末的胶囊。或者，也可以是使用合适的推进剂、例如氯氟烃、氢氟烃或二氧化碳等合适的气体的加压气溶胶喷雾剂等形态。

[0233] 通常，在口服给药的情况下，1 天的给药量合适的是每单位体重约 0.001 ～ 100mg/kg，较好为 0.1 ～ 30mg/kg，更好为 0.1 ～ 10mg/kg，该量可以一次性给予或者分 2 ～ 4 次给予。在静脉内给药的情况下，1 天的给药量合适的是每单位体重约 0.0001 ～ 10mg/kg，可 1 天 1 次～分数次给药。作为经粘膜剂，可 1 天 1 次～分数次给予每单位体重约 0.001 ～ 100mg/kg。给药量可考虑症状、年龄、性别等根据各种不同的情况适当决定。

[0234] 式 (I) 的化合物可与认为所述式 (I) 的化合物显示出有效性的疾病的各种治疗或预防剂并用。该并用可以是同时给药、分别连续给药、或隔所需的时间间隔给药。同时给药制剂既可以是配合剂，也可以分别制剂化。

[0235] （实施例）

[0236] 以下，基于实施例对式（I）的化合物及其原料化合物的制造方法进行更详细的说明。本发明不限于下述实施例中记载的化合物。原料化合物的制法示于制造例。式（I）的化合物的制造方法不仅限于以下所示的具体实施例的制造方法，式（I）的化合物也可通过这些制造方法的组合或对本领域技术人员来说显而易见的方法来制造。

[0237] 制造例、实施例及下述表中采用以下缩写。

[0238] PEx：制造例编号、Ex：实施例编号、Syn：通过同样的方法制得的实施例编号、PSyn：通过同样的方法制得的制造例编号、NO：化合物编号、Str：结构式、DATA：物理化学数据、EI+：质谱的 m/z 值（离子化方法 EI，如无特别说明则表示 $(M)^+$）、ESI+：质谱的 m/z 值（离子化方法 ESI，如无特别说明则表示 $(M+H)^+$）、ESI-：m/z 值（离子化方法 ESI，如无特别说明则表示 $(M-H)^-$）、FAB+：质谱的 m/z 值（如无特别说明则表示 $(M+H)^+$）、NMR1：DMSO-d_6 中的 ^{1}H NMR 中的 δ（ppm）、NMR2：$CDCl_3$ 中的 ^{1}H NMR 中的 δ（ppm）、NMR3：CD_3OD 中的 ^{1}H NMR 中的 δ（ppm）、s：单峰（波谱）、d：双峰（波谱）、t：三重峰（波谱）、q：四重峰（波谱）、br：宽峰（波谱）（例：br-s）、RT：HPLC 中的保留时间（分钟）。结构式中的 HCl 表示盐酸盐，HCl 之前的数字表示摩尔比。例如 2HCl 是指二盐酸盐。

[0239] 制造例 1

[0240] 在 4,6- 二氯 -2-（甲基硫烷基（スルファニル））嘧啶（5g）的 N，N- 二甲基甲酰胺（50mL）溶液中添加碳酸钾（5.3g）和 2-（二氟甲基）-1H- 苯并咪唑（3.9g），将混合物在室温下搅拌 5 小时。在反应混合物中加水（300mL），用乙酸乙酯（300mL）萃取。用饱和食盐水洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用硅胶柱色谱法（己烷：乙酸乙酯＝ 90 ： 10 ～ 40 ： 60）纯化，以白色粉末的形式得到 1-[6- 氯 -2-（甲基硫烷基）嘧啶 -4- 基]-2-（二氟甲基）-1H- 苯并咪唑（5.49g）。

[0241] 制造例 2

[0242] 在 1-[6- 氯 -2-（甲基硫烷基）嘧啶 -4- 基]-2-（二氟甲基）-1H- 苯并咪唑（2.2g）的 N，N- 二甲基甲酰胺（11mL）溶液中添加碳酸钾（1.4g）和吗啉（0.88mL），将混合物在室温下搅拌 1 小时。在反应混合物中加水（150mL），用乙酸乙酯（150mL）萃取。用饱和食盐水（150mL）洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用硅胶柱色谱法（己烷：乙酸乙酯＝ 70 ： 30 ～ 50 ： 50）纯化，以白色粉末的形式得到 2-（二氟甲基）-1-[2-（甲基硫烷基）-6- 吗啉 -4- 基嘧啶 -4- 基]-1H- 苯并咪唑（2.1g）。

[0243] 制造例 3

[0244] 在 2-（二氟甲基）-1-[2-（甲基硫烷基）-6- 吗啉 -4- 基嘧啶 -4- 基]-1H- 苯并咪唑（3g）的二氯甲烷（60mL）溶液中在冰冷下添加间氯过苯甲酸（75%，含水）（1.9g），将混合物在 0℃下搅拌 15 分钟。在反应混合物中添加饱和碳酸氢钠水溶液，用二氯甲烷（200mL）萃取。用水（200mL）、饱和食盐水（200mL）洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用硅胶柱色谱法（氯仿：甲醇＝ 100 ： 0 ～ 98 ： 2）纯化，以淡黄色无定形物质的形式得到 2-（二氟甲基）-1-[2-（甲基亚硫酰基）-6- 吗啉 -4- 基嘧啶 -4- 基]-1H- 苯并咪唑（2.8g）。该化合物的硅胶 TLC（氯仿：甲醇＝ 10 ： 1）中的 Rf 值为 0.56。

[0245] 制造例 4

[0246] 在 2-（二氟甲基）-1-[2-（甲基硫烷基）-6- 吗啉 -4- 基嘧啶 -4- 基]-1H- 苯并咪唑

(2.1g) 的二氯甲烷 (21mL) 溶液中在冰冷下添加间氯过苯甲酸 (75%，含水) (2.7g)，将混合物在 0℃下搅拌 15 分钟。在反应混合物中添加饱和碳酸氢钠水溶液，用二氯甲烷 (200mL) 萃取。用水 (200mL)、饱和食盐水 (200mL) 洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用硅胶柱色谱法 (氯仿：甲醇＝ 100 ： 0 ～ 98 ： 2) 纯化，以淡黄色无定形物质的形式得到 2-(二氟甲基)-1-[2-(甲基磺酰基)-6- 吗啉 -4- 基嘧啶 -4- 基]-1H- 苯并咪唑 (2.27g)。该化合物的硅胶 TLC(氯仿：甲醇＝ 10 ： 1) 中的 Rf 值为 0.67。

[0247] 制造例 5

[0248] 在 1-[6- 氯 -2-(甲基硫烷基) 嘧啶 -4- 基]-2-(二氟甲基)-1H- 苯并咪唑 (150mg) 的 N,N- 二甲基乙酰胺 (2mL) 溶液中添加 (反 -4- 羟基环己基) 氨基甲酸叔丁酯 (125mg)、碳酸铯 (225mg)，将混合物在室温下搅拌 1 小时，在 60℃下搅拌 1 小时，在 120℃下搅拌 3 小时。在反应混合物中注入水 (20mL)，用己烷：乙酸乙酯 (1 ： 1,100mL) 萃取。用水、饱和食盐水洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用硅胶柱色谱法 (己烷：乙酸乙酯＝ 90 ： 10 ～ 60 ： 40) 纯化，从而以白色无定形物质的形式得到 [反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2-(甲基硫烷基) 嘧啶 -4- 基 } 氧基) 环己基] 氨基甲酸叔丁酯 (129mg)。

[0249] 制造例 6

[0250] 在 4- 氟苯 -1,2- 二胺 (1.00g) 中添加二氟乙酸 (1mL)，将混合物在 90℃下搅拌 6 小时。将反应混合物注入水 (20mL) 中，添加乙酸乙酯 (20mL)。用 1M 氢氧化钠水溶液将混合物调整至碱性后，用乙酸乙酯 (50mL) 萃取。用水、饱和食盐水洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，用硅胶柱色谱法 (己烷：乙酸乙酯＝ 70 ： 30 ～ 0 ： 100) 纯化，从而以白色粉末的形式得到 2-(二氟甲基)-5- 氟 -1H- 苯并咪唑 (1.22g)。

[0251] 制造例 7

[0252] 在 4,6- 二氯 -2-(甲基硫烷基) 嘧啶 (1.4g) 和 2-(二氟甲基)-5- 氟 -1H- 苯并咪唑 (1.2g) 的 N, N- 二甲基甲酰胺 (28mL) 溶液中添加碳酸钾 (1.48g)，将混合物在室温下搅拌过夜。在反应混合物中加水 (100mL)，用乙酸乙酯 (200mL) 萃取。用水、饱和食盐水洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，用硅胶柱色谱法 (己烷：乙酸乙酯＝ 95 ： 5 ～ 70 ： 30) 纯化，从而以白色粉末的形式分别得到两种化合物。

[0253] 1-[6- 氯 -2-(甲基硫烷基) 嘧啶 -4- 基]-2-(二氟甲基)-5- 氟 -1H- 苯并咪唑：319mg，硅胶 TLC(己烷：乙酸乙酯＝ 5 ： 1) 中的 Rf 值为 0.51。

[0254] 1-[6- 氯 -2-(甲基硫烷基) 嘧啶 -4- 基]-2-(二氟甲基)-6- 氟 -1H- 苯并咪唑：438mg，硅胶 TLC(己烷：乙酸乙酯＝ 5 ： 1) 中的 Rf 值为 0.46。

[0255] 制造例 8

[0256] 将 60%氢化钠 (417mg) 悬浮于四氢呋喃 (24mL)，添加 (反 -4- 羟基环己基) 氨基甲酸叔丁酯 (1.87g)、15- 冠 -5(1.73mL)，将混合物在室温下搅拌 30 分钟。在反应混合物中添加 4,6- 二氯 -2-(甲基磺酰基) 嘧啶 (1.97g)，于 60℃搅拌过夜。将反应混合物注入饱和氯化铵水溶液 (100mL)，用乙酸乙酯 (200mL) 萃取。用水、饱和食盐水洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，用硅胶柱色谱法 (己烷：乙酸乙酯＝ 93 ： 7 ～ 70 ： 30) 纯化，从而以白色粉末的形式得到 { 反 -4-[(4,6- 二氯嘧啶 -2- 基) 氧基] 环己基 } 氨基甲酸叔丁酯 (598mg)。

[0257] 制造例 16

[0258] 将 60％氢化钠 (288mg) 悬浮于二甲氧基乙烷 (15mL)，添加 [反 -4-(羟甲基) 环己基] 氨基甲酸叔丁酯 (750mg)、1，4，7，10，13- 五氧杂环十五烷，在室温下搅拌 30 分钟。接着，添加 4，6- 二氯 -2-(甲基磺酰基) 嘧啶 (743mg)，于 80℃搅拌过夜。将反应混合物注入饱和氯化铵水溶液 (50mL)，用乙酸乙酯 (200mL) 萃取，用水、饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。用硅胶柱色谱法 (己烷：乙酸乙酯＝ 95 ： 5 ～ 85 ： 15) 纯化，以白色粉末的形式得到目标化合物 (反 -4-{[(4，6- 二氯嘧啶 -2- 基) 氧基] 甲基 } 环己基) 氨基甲酸叔丁酯 (290mg)。

[0259] 制造例 23

[0260] 将 2-(二氟甲基)-1-[6-(1，4- 二氧杂螺 [4.5] 癸 -8- 基甲氧基)-2-(甲基硫烷基) 嘧啶 -4- 基]-1H- 苯并咪唑 (1.3g) 溶于二氯甲烷 (20mL)，在 0℃下添加间氯过苯甲酸 (75％，含水)(712mg)，搅拌 30 分钟。在反应混合物中添加饱和碳酸氢钠水溶液 (30mL)，用氯仿 (100mL) 萃取，用水、饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。将残渣溶于二甲基甲酰胺 (10mL)，添加吗啉 (1.22mL)，在室温下搅拌 2 小时。将反应混合物注入水 (50mL) 中，用乙酸乙酯 (200mL) 萃取，用水、饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。用硅胶柱色谱法 (己烷：乙酸乙酯＝ 95 ： 5 ～ 80 ： 20) 纯化，以白色粉末的形式得到目标化合物 2-(二氟甲基)-1-[6-(1，4- 二氧杂螺 [4.5] 癸 -8- 基甲氧基)-2-(吗啉 -4- 基) 嘧啶 -4- 基]-1H- 苯并咪唑 (1.21g)。

[0261] 制造例 24

[0262] 将 2-(二氟甲基)-1-[6-(1，4- 二氧杂螺 [4.5] 癸 -8- 基甲氧基)-2-(吗啉 -4- 基) 嘧啶 -4- 基]-1H- 苯并咪唑 (1.2g) 溶于四氢呋喃 (12mL)- 水 (12mL)，在室温下添加 4- 甲基苯磺酸一水合物 (2.27g)，搅拌 3 小时。在反应混合物中添加饱和碳酸氢钠水溶液 (30mL)，用乙酸乙酯 (100mL) 萃取，用水、饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。用硅胶柱色谱法 (己烷：乙酸乙酯＝ 80 ： 20 ～ 40 ： 60) 纯化，以白色粉末的形式得到目标化合物 4-[({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2-(吗啉 -4- 基) 嘧啶 -4- 基 } 氧基) 甲基] 环己酮 (941mg)。

[0263] 实施例 1

[0264] 在 2-(二氟甲基)-1-[2-(甲基磺酰基)-6- 吗啉 -4- 基嘧啶 -4- 基]-1H- 苯并咪唑 (2.27g) 的 N，N- 二甲基乙酰胺 (57mL) 溶液中添加反 - 环己烷 -1，4- 二胺 (5.45g) 和碳酸钾 (1.15g)，将混合物在 100℃下搅拌 1 小时。将反应混合物冷却至室温后加水 (300mL)，用乙酸乙酯 (300mL) 萃取。用饱和食盐水 (200mL) 洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 25 ： 75 ～ 0 ： 100，然后是氯仿：甲醇＝ 100 ： 0 ～ 97 ： 3) 纯化，以淡黄色粉末的形式得到反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 环己烷 -1，4- 二胺 (2.21g)。

[0265] 实施例 2

[0266] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1，3，5- 三嗪 -2- 基 } 环己烷 -1，4- 二胺 (50mg) 的 N，N- 二甲基甲酰胺溶液中添加甲氧基乙酸 (9μL) 和 1- 羟基苯并三唑 (15mg)、N-[3-(二甲基氨基) 丙基]-N′ - 乙基碳二亚胺盐酸盐 (22mg)，将混合物在室温下搅拌过夜。在反应混合物中加水 (50mL)，用乙酸乙酯 (50mL)

萃取。用饱和食盐水洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，滤取生成的固体，用乙酸乙酯洗涤，从而以白色粉末的形式得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 氨基) 环己基]-2- 甲氧基乙酰胺 (32mg)。

[0267] 实施例 3

[0268] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 环己烷 -1,4- 二胺 (50mg) 的二氯甲烷 (1.25mL) 溶液中添加三乙胺 (47μL) 和丙烷 -1- 磺酰氯 (12μL)，将混合物在室温下搅拌过夜。在反应混合物中加水 (50mL)，用乙酸乙酯 (50mL) 萃取。用饱和食盐水 (50mL) 洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50 ～ 0 : 100) 纯化，以白色粉末的形式得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 氨基) 环己基] 丙烷 -1- 磺酰胺 (46mg)。

[0269] 实施例 4

[0270] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 环己烷 -1,4- 二胺 (250mg) 的二氯甲烷 (4.5mL) 溶液中添加 37％甲醛水溶液 (0.443mL) 和三乙酰氧基硼氢化钠 (476mg)，将混合物在室温下搅拌 1 小时。在反应混合物中加水 (30mL)，用氯仿 (100mL) 萃取。用饱和食盐水洗涤有机层，用无水硫酸钠干燥。减压蒸除溶剂后，将残渣用氨基硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50 ～ 90 : 10) 纯化，从而以白色粉末的形式得到反 -N′ -{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 }-N,N- 二甲基环己烷 -1,4- 二胺 (216mg)。

[0271] 实施例 5

[0272] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 环己烷 -1,4- 二胺 (30mg) 的二氯甲烷 (1.2mL) 溶液中添加异氰酸甲酯 (4.2μL)，将混合物在室温下搅拌 0.5 小时。将反应混合物减压浓缩后，用硅胶柱色谱法 (氯仿) 纯化，以白色粉末的形式得到 1-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 氨基) 环己基]-3- 甲基脲 (28mg)。

[0273] 实施例 6

[0274] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 环己烷 -1,4- 二胺 (70mg) 的 N,N- 二甲基甲酰胺 (1.4mL) 溶液中添加三乙胺 (44μL) 和 1,1′ - 羰基双 (1H- 咪唑)(26mg)，将混合物在室温下搅拌 1 小时。通过质谱确认反应的进行后，在反应混合物中添加 2-(吗啉 -4- 基) 乙胺 (25μL)，在室温下搅拌 3 小时。在反应混合物中加水 (20mL)，用氯仿 (10mL) 萃取。用无水硫酸镁干燥有机层。减压蒸除溶剂后，将残渣用硅胶柱色谱法 (氯仿 : 甲醇 = 20 : 80) 纯化，以白色粉末的形式得到 1-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 氨基) 环己基]-3-(2- 吗啉 -4- 基乙基) 脲 (62mg)。

[0275] 实施例 7

[0276] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 环己烷 -1,4- 二胺 (1.86g) 的二氯甲烷 (37mL) 溶液中添加三乙胺 (1.46mL) 和二碳酸二叔丁酯 (1.1g)，将混合物在室温下搅拌 1 小时。在反应混合物中加水 (50mL)，用乙酸乙酯 (50mL) 萃取。用饱和食盐水 (50mL) 洗涤有机层，用无水硫酸镁干燥。减压蒸除

溶剂后，将残渣用硅胶柱色谱法（己烷：乙酸乙酯＝80 ： 20 ～ 50 ： 50）纯化，以白色粉末的形式得到［反 -4-（{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基｝氨基）环己基］氨基甲酸叔丁酯（2.04g）。

[0277] 实施例 8

[0278] 在（2-{［反 -4-（{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基｝氨基）环己烷］氨基}-2- 氧代乙基）氨基甲酸叔丁酯（138mg）的 1,4- 二噁烷（1.4mL）溶液中添加 4M 氯化氢 /1,4- 二噁烷溶液（574μL），将混合物在室温下搅拌 2 小时。在反应混合物中添加 2M 氨 / 乙醇溶液（2mL）并减压浓缩，将残渣用氨基硅胶柱色谱法（己烷：乙酸乙酯＝50 ： 50 ～ 0 ： 100，然后是氯仿：甲醇＝100 ： 0 ～ 98 ： 2）纯化，以白色粉末的形式得到 N-［反 -4-（{4-[2-（二氟甲基）-1H- 苯并三唑 -1- 基］-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基｝氨基）环己基］甘氨酰胺（74mg）。

[0279] 实施例 9

[0280] 在反 -N-{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基｝环己烷 -1,4- 二胺（200mg）的二氯甲烷（2mL）溶液中在冰冷下添加三乙胺（63μL）和溴乙酰氯（37μL），将混合物在 0℃下搅拌 30 分钟。在反应混合物中加水（50mL），用乙酸乙酯（50mL）萃取。用饱和食盐水（50mL）洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，滤取生成的固体，用异丙醚洗涤，从而以白色粉末的形式得到 2- 溴 -N-［反 -4-（{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基｝氨基）环己基］乙酰胺（207mg）。

[0281] 实施例 10

[0282] 在反 -N-{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基｝环己烷 -1,4- 二胺（300mg）的 N，N- 二甲基乙酰胺（6mL）溶液中添加三乙胺（0.261mL）和双（2- 溴乙基）醚（0.12mL），将混合物在 70℃下搅拌过夜。在反应混合物中追加三乙胺（0.261mL）和双（2- 溴乙基）醚（0.12mL），在 70 度下搅拌过夜。在反应混合物中加水（30mL），用乙酸乙酯（100mL）萃取。用水、饱和食盐水洗涤有机层，用无水硫酸钠干燥。减压蒸除溶剂后，将残渣用氨基硅胶柱色谱法（己烷：乙酸乙酯＝50 ： 50 ～ 80 ： 20）纯化，从而以白色粉末的形式得到 4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基 -N-（反 -4- 吗啉 -4- 基环己基）-1,3,5- 三嗪 -2- 胺（231mg）。

[0283] 实施例 11

[0284] 在反 -N-{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基嘧啶 -2- 基｝环己烷 -1,4- 二胺（50mg）的二氯甲烷（1mL）溶液中添加三乙胺（0.047mL）和 4- 氯丁酰氯（0.014mL），将混合物在冰冷下搅拌 1 小时。将反应混合物浓缩后，将残渣溶于 N,N- 二甲基甲酰胺（5mL），添加 60％氢化钠（13.5mg），在 0℃下搅拌 30 分钟，在室温下搅拌 1 小时。在反应混合物中加水（30mL），用乙酸乙酯（100mL）萃取。用水、饱和食盐水洗涤有机层，用无水硫酸镁干燥。减压蒸除溶剂后，将残渣用氨基硅胶柱色谱法（己烷：乙酸乙酯＝50 ： 50 ～ 100 ： 0）纯化，从而以白色粉末的形式得到 1-［反 -4-（{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基嘧啶 -2- 基｝氨基）环己基］吡咯烷 -2- 酮（40mg）。

[0285] 实施例 12

[0286] 在 2- 溴 -N-［反 -4-（{4-[2-（二氟甲基）-1H- 苯并咪唑 -1- 基］-6- 吗啉 -4- 基 -1,

3,5- 三嗪 -2- 基 } 氨基) 环己基] 乙酰胺 (50mg) 的 1,3- 二甲基 -2- 咪唑啉酮 (0.5mL) 溶液中添加碳酸钾 (24mg) 和吡咯烷 (15μL),将混合物在室温下搅拌 1 小时。在反应混合物中加水 (50mL),用乙酸乙酯 (50mL) 萃取。用饱和食盐水 (50mL) 洗涤有机层,用无水硫酸镁干燥。减压蒸除溶剂后,将残渣用硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50 ~ 0 : 100,然后是氯仿 : 甲醇 = 100 : 0 ~ 90 : 10) 纯化,以白色粉末的形式得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 氨基) 环己基]-2- 吡咯烷 -1- 基乙酰胺 (49mg)。

[0287] 实施例 13

[0288] 在 60 % 氢化钠 (2.8mg) 的 N,N- 二甲基甲酰胺 (1mL) 悬浮液中添加 3- 氯 -N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 氨基) 环己基] 丙烷 -1- 磺酰胺 (35mg),将混合物在 0℃下搅拌 1 小时,在室温下搅拌 2 小时。在反应混合物中加水 (20mL),用乙酸乙酯 (100mL) 萃取。用水、饱和食盐水洗涤有机层,用无水硫酸钠干燥。减压蒸除溶剂后,将残渣用硅胶柱色谱法 (己烷 : 乙酸乙酯 = 60 : 50 ~ 100 : 0) 纯化,从而以白色粉末的形式得到 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-[反 -4-(1,1- 二氧化异噻唑啉 -2- 基) 环己基]-6- 吗啉 -4- 基嘧啶 -2- 胺 (31.6mg)。

[0289] 实施例 14

[0290] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 }-N′ - 甲基环己烷 -1,4- 二胺 (53mg) 的吡啶 (468μL) 溶液中添加乙酸酐 (14μL),将混合物在室温下搅拌 1 小时。在反应液中加水 (50mL),用乙酸乙酯 (50mL) 萃取。用饱和食盐水 (50mL) 洗涤有机层,用无水硫酸镁干燥。减压蒸除溶剂后,滤取生成的固体,用异丙醚洗涤,从而以白色粉末的形式得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 氨基) 环己基]-N- 甲基乙酰胺 (55mg)。

[0291] 实施例 15

[0292] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 环己烷 -1,4- 二胺 (1g) 的乙醇 (20mL) 溶液中添加 1H-1,2,3- 苯并三唑 -1- 基甲醇 (336mg),将混合物在室温下搅拌 1 小时。在反应混合物中添加四氢硼酸钠 (170mg),在室温下搅拌 1 小时。在反应混合物中添加饱和碳酸氢钠水溶液 (200mL),用乙酸乙酯 (200mL) 萃取。用饱和食盐水 (200mL) 洗涤有机层,用无水硫酸镁干燥。减压蒸除溶剂后,将残渣用氨基硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50 ~ 0 : 100,然后是氯仿 : 甲醇 = 100 : 0 ~ 98 : 2) 纯化,以白色粉末的形式得到反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 }-N′ - 甲基环己烷 -1,4- 二胺 (890mg)。

[0293] 实施例 16

[0294] 将 N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基]-N,N- 二甲基甘氨酰胺 (100mg) 溶于二氯甲烷 (20mL)- 甲醇 (4mL) 混合溶剂,添加 2M 氯化氢 / 乙醇溶液 (0.3mL),在室温下搅拌 10 分钟。减压蒸除溶剂,在残渣中添加甲醇 (30mL),再次蒸除溶剂。滤取生成的固体,用异丙醚洗涤,以白色粉末的形式得到 N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基]-N,N- 二甲基甘氨酰胺盐酸盐 (93mg)。

[0295] 实施例 17

[0296] 在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基} 环己烷 -1,4- 二胺 (65mg) 的二氯甲烷 (1.3mL) 溶液中添加三乙胺 (20μL) 和 3- 溴丙酰氯 (25mg),将混合物在室温下搅拌 30 分钟。在反应混合物中加水 (50mL),用乙酸乙酯 (50mL) 萃取。用饱和食盐水 (50mL) 洗涤有机层,用无水硫酸镁干燥。减压蒸除溶剂后,滤取生成的固体,用乙酸乙酯洗涤。

[0297] 将该固体溶于 1,3- 二甲基 -2- 咪唑啉酮 (1.3mL),添加碳酸钾 (61mg) 和吡咯烷 (18μL),在室温下搅拌 2 小时。在反应混合物中加水 (50mL),用乙酸乙酯 (50mL) 萃取。用饱和食盐水 (50mL) 洗涤有机层,用无水硫酸镁干燥。减压蒸除溶剂后,将残渣用硅胶柱色谱法 (己烷:乙酸乙酯= 50 : 50 ~ 0 : 100,然后是氯仿:甲醇= 100 : 0 ~ 90 : 10) 纯化,以白色粉末的形式得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基} 氨基) 环己基]-3- 吡咯烷 -1- 基丙酰胺 (13mg)。

[0298] 实施例 18

[0299] 在冰冷下在反 -N-{6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基} 环己烷 -1,4- 二胺 (100mg)、吡啶 (0.04mL) 和二氯甲烷 (1mL) 的混合物中添加 3- 氯丙烷 -1- 磺酰氯 (0.04mL),在室温下搅拌过夜。将反应混合物浓缩,对残渣实施氨基硅胶柱色谱法 (己烷:乙酸乙酯= 50 : 50 ~ 0 : 100),收集并浓缩目标馏分。将残渣溶于 N,N- 二甲基甲酰胺 (1mL),添加 60% 氢化钠 (27mg),在 0℃下搅拌 1 小时,在室温下搅拌 2 小时。将反应混合物注入饱和氯化铵水溶液,用乙酸乙酯 (100mL) 萃取。用水、饱和食盐水洗涤有机层,用无水硫酸钠干燥。减压蒸除溶剂后,将残渣用硅胶柱色谱法 (己烷:乙酸乙酯= 60 : 40 ~ 0 : 100) 纯化,从而以淡褐色粉末的形式得到 6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-[反 -4-(1,1- 二氧化异噻唑啉 -2- 基) 环己基]-2- 吗啉 -4- 基嘧啶 -4- 胺 (27mg)。

[0300] 实施例 19

[0301] 在 [(1R)-3-(苄氧基)-1-{[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基} 氨基) 环己基] 氨基甲酰基} 丙基] 氨基甲酸叔丁酯 (180mg) 的甲醇 (3mL) 溶液中添加 10% 钯 - 碳 (50%,含水),在 1 个大气压的氢气气氛下搅拌 9 小时。将反应混合物用硅藻土 (Celite) 过滤,然后浓缩。将残渣用硅胶柱色谱法 (己烷:乙酸乙酯= 40 : 60 ~ 0 : 100) 纯化,从而以白色粉末的形式得到 [(1R)-1-{[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基} 氨基) 环己基] 氨基甲酰基}-3- 羟丙基] 氨基甲酸叔丁酯 (143mg)。

[0302] 实施例 20

[0303] 在反 -N-{6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基} 环己烷 -1,4- 二胺 (40mg) 的 N,N- 二甲基甲酰胺 (0.4mL) 溶液中添加 N-(叔丁氧基羰基)-2- 甲基丙氨酸 (21mg)、1-[双 (二甲基氨基) 亚甲基]-1H-1,2,3- 三唑并 [4,5-b] 吡啶鎓 -3- 氧化物六氟磷酸盐 (HATU)(51mg)、N,N- 二异丙基乙胺 (0.079mL),将混合物在室温下搅拌 3 小时。在反应混合物中加水 (20mL)。滤取生成的粉末,用异丙醚洗涤,减压干燥,从而以白色粉末的形式得到 (2-{[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基} 氨基) 环己基] 氨基}-1,1- 二甲基 -2- 氧代乙基) 氨基甲酸叔丁

酯 (56mg)。

[0304] 实施例 21

[0305] 在 (3R)-N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基] 哌啶 -3- 甲酰胺 (50mg) 的二氯甲烷 (1mL) 溶液中添加 37% 甲醛水溶液 (0.022mL),在室温下搅拌 30 分钟。在反应混合物中添加三乙酰氧基硼氢化钠 (57mg),在室温下搅拌 2 小时。在反应混合物中添加饱和碳酸氢钠水溶液 (5mL) 和水 (5mL),用氯仿 (100mL) 萃取。用水、饱和食盐水洗涤有机层,用无水硫酸钠干燥。减压蒸除溶剂后,将残渣用氨基硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50) 纯化,收集并浓缩目标馏分。将残渣溶于甲醇,添加 4M 氯化氢 /1,4- 二噁烷溶液,在室温下搅拌 10 分钟,然后浓缩,以白色粉末的形式得到 (3R)-N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基]-1- 甲基哌啶 -3- 甲酰胺盐酸盐 (41mg)。

[0306] 实施例 22

[0307] 在 0℃下在 [反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2-(甲基硫烷基) 嘧啶 -4- 基 } 氨基) 环己基] 氨基甲酸叔丁酯 (7.6g) 的氯仿 (76mL) 溶液中添加间氯过苯甲酸 (75%,含水)(3.81g),搅拌 20 分钟。在反应混合物中添加饱和碳酸氢钠水溶液 (50mL),用氯仿 (200mL) 萃取。用水、饱和食盐水洗涤有机层,用无水硫酸钠干燥。减压蒸除溶剂后,将残渣溶于 N, N- 二甲基乙酰胺 (40mL),添加吗啉 (6.57mL),在 100℃下搅拌 3 小时。将反应混合物注入水 (200mL) 中,用乙酸乙酯 (500mL) 萃取。用水、饱和食盐水洗涤有机层,用无水硫酸镁干燥。减压蒸除溶剂后,将残渣用硅胶柱色谱法 (己烷 : 乙酸乙酯 = 70 : 30 ～ 0 : 100) 纯化,从而以白色粉末的形式得到 [反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基] 氨基甲酸叔丁酯 (7.88g)。

[0308] 实施例 23

[0309] 在反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氧基) 环己胺 (40mg) 的 N,N- 二甲基乙酰胺 (1mL) 溶液中添加三乙胺 (0.05mL) 和双 (2- 溴乙基) 醚 (0.025mL),通过微波照射对混合物加热并在 120℃下搅拌 1.5 小时。在反应混合物中加水 (30mL),用乙酸乙酯 (100mL) 萃取。用水、饱和食盐水洗涤有机层,用无水硫酸钠干燥。减压蒸除溶剂后,将残渣用氨基硅胶柱色谱法 (己烷 : 乙酸乙酯 = 60 : 40 ～ 20 : 80) 纯化,收集并浓缩目标馏分。将残渣溶于甲醇,添加 4M 氯化氢 /1,4- 二噁烷溶液,在室温下搅拌 10 分钟,然后浓缩,以白色粉末的形式得到 2-(二氟甲基)-1-{2- 吗啉 -4- 基 -6-[(反 -4- 吗啉 -4- 基环己基) 氧基] 嘧啶 -4- 基 }-1H- 苯并咪唑盐酸盐 (36mg)。

[0310] 实施例 24

[0311] 在反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氧基) 环己胺 (50mg) 的 N, N- 二甲基甲酰胺 (0.5mL) 溶液中添加 N, N- 二甲基甘氨酸 (13mg)、1- 羟基苯并三唑 (17mg) 和 N-[3-(二甲基氨基) 丙基]-N′ - 乙基碳二亚胺盐酸盐 (24mg),将混合物在室温下搅拌过夜。在反应混合物中加水 (50mL),用乙酸乙酯 (100mL) 萃取。用饱和食盐水洗涤有机层,用无水硫酸钠干燥。减压蒸除溶剂后,将残渣用氨基硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50 ～ 0 : 100) 纯化,收集并浓缩目标馏分。将残渣溶于氯仿 (1mL)- 甲醇 (0.5mL),添加 4M 氯化氢 /1,4- 二噁烷溶液 (0.2mL),在室温下搅拌 10 分钟,然后浓缩,以白色粉末的形式得到 N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并

咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氧基) 环己基]-N, N- 二甲基甘氨酰胺盐酸盐 (41mg)。

[0312] 实施例 25

[0313] 在反 -4-[({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氧基) 甲基] 环己胺 (55mg) 的甲醇 (1.65mL) 溶液中添加二乙烯砜 (0.012mL),将混合物在室温下搅拌过夜。将反应混合物浓缩,将残渣用硅胶柱色谱法 (氯仿 : 甲醇 = 100 : 0 ~ 98 : 2) 纯化,收集并浓缩目标馏分。将残渣溶于氯仿 (1mL)- 甲醇 (0.5mL),添加 4M 氯化氢 /1,4- 二噁烷溶液 (0.2mL),在室温下搅拌 10 分钟,然后浓缩,以白色粉末的形式得到 2-(二氟甲基)-1-(6-{[反 -4-(1,1- 二氧化硫代吗啉 -4- 基) 环己基] 甲氧基 }-2- 吗啉 -4- 基嘧啶 -4- 基)-1H- 苯并咪唑盐酸盐 (71mg)。

[0314] 实施例 26

[0315] 在 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-{[反 -4-(甲基氨基) 环己基] 甲基 }-6- 吗啉 -4- 基嘧啶 -2- 胺 (80mg) 的 N, N- 二甲基乙酰胺 (0.8mL) 溶液中添加 1- 溴 -2- 氟乙烷 (26mg) 和碳酸钾 (52mg),通过微波照射对混合物加热,将其在 100℃下搅拌 1 小时。在反应混合物中加水 (50mL),用乙酸乙酯 (50mL) 萃取。用饱和食盐水 (50mL) 洗涤有机层,用无水硫酸镁干燥。减压蒸除溶剂后,将残渣用硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50) 纯化,以无色油状物的形式得到 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-({ 反 -4-[(2- 氟乙基)(甲基) 氨基] 环己基 } 甲基)-6- 吗啉 -4- 基嘧啶 -2- 胺 (34mg)。

[0316] 实施例 225

[0317] 将 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 氨基) 环己基]-3-(4- 碘苯基) 丙酰胺 (80mg) 溶于二甲基甲酰胺 (800μl),添加氰化锌 (40mg)、三 (二亚苄基丙酮) 二钯 (0)(16mg)、1,1′ - 双 (二苯基膦基) 二茂铁 (13mg),在 120℃下搅拌 4 小时。通过硅藻土过滤除去 Pd。在滤液中加水 (10mL),用乙酸乙酯 (15mL) 萃取后,用饱和食盐水洗涤。用无水硫酸镁干燥有机层,减压蒸除溶剂后,将残渣用氨基硅胶柱色谱法 (己烷 : 乙酸乙酯 = 40 : 60) 纯化,以褐色油状物的形式得到 3-(4- 氰基苯基)-N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 氨基) 氰基己基] 丙酰胺 (41mg)。

[0318] 实施例 239

[0319] 将 N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基] 乙烯磺酰胺 (100mg) 和吡咯烷 (155μl) 的混合物溶于异丙醇 (1.6mL),用微波反应装置在 170℃下搅拌 7 分钟。将反应混合物浓缩,将残渣溶于乙酸乙酯 (10mL),添加饱和氯化铵 (10mL),用乙酸乙酯 (100mL) 萃取。用水、饱和食盐水洗涤有机层,用无水硫酸钠干燥。减压蒸除溶剂后,用氨基硅胶柱色谱法 (氯仿 : 甲醇 = 100 : 0 ~ 99 : 1) 纯化。浓缩目标馏分,将残渣溶于甲醇 (1mL),添加 4M 氯化氢 /1,4- 二噁烷溶液 (0.05mL),在室温下搅拌 10 分钟,然后浓缩。从而以白色粉末的形式得到 N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基]-2- 吡咯烷 -1- 基乙磺酰胺盐酸盐 (105mg)。

[0320] 实施例 245

[0321] 将 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基-N-{[反-4-(四氢-2H-噻喃-4-基氨基)环己基]甲基}嘧啶-2-胺(64mg)溶于二氯甲烷(1.3mL),在0℃下添加间氯过苯甲酸(75%,含水)(83mg),在室温下搅拌1.5小时。在反应混合物中添加饱和碳酸氢钠水溶液(10mL),用氯仿(15mL)萃取,用水、饱和食盐水洗涤。用无水硫酸镁干燥有机层。减压蒸除溶剂后,将残渣用氨基硅胶柱色谱法(氯仿:甲醇=1000:0～0:100)纯化,以白色粉末的形式得到4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基-N-{[反-4-(1-氧化四氢-2H-噻喃-4-基氨基)环己基]甲基}嘧啶-2-胺(27mg)。

[0322] 实施例258

[0323] 将N-{[反-4-(氨基甲基)环己基]甲基}-4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基吡啶-2-胺(80mg)溶于甲醇(2.4mL),添加二乙烯砜(17μl),在室温下搅拌3小时。将反应混合物浓缩,将残渣用氨基硅胶柱色谱法(仅乙酸乙酯)纯化,以白色粉末的形式得到4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(1,1-二氧化硫代吗啉-4-基)甲基]环己基}甲基)-6-吗啉-4-基吡啶-2-胺(40mg)。

[0324] 实施例275

[0325] 将4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2-甲氧基乙基)氨基]环己基}甲基)-6-吗啉-4-基吡啶-2-胺(70mg)溶于甲醇(1.4mL),添加分子筛4A(100mg)、[(1-乙氧基环丙基)氧基](三甲基)硅烷(163μl)、三氰基硼氢化钠(54mg)、乙酸(78μl),在氮气气氛下、在加热回流下搅拌5小时。添加饱和碳酸氢钠水溶液(10mL),用乙酸乙酯(15mL)萃取。用无水硫酸镁干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=90:10～40:60)纯化,以白色粉末的形式得到N-({反-4-[环丙基(2-甲氧基乙基)氨基]环己基}甲基)-4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基吡啶-2-胺(9.7mg)。

[0326] 实施例279

[0327] 将4-[2-(二氟甲基)-1H-二苯并咪唑-1-基]-N-{[反-4-(甲基氨基)环己基]甲基}-6-吗啉-4-基吡啶-2-胺(80mg)溶于N-甲基吡咯烷酮(800μl),添加碳酸钾(130mg)和2,2-二氟乙基三氟甲磺酸酯(109mg),用微波反应装置在200℃下搅拌1小时。加水(10mL),用乙酸乙酯(15mL)萃取后,用饱和食盐水洗涤。用无水硫酸镁干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=30:70～60:40)纯化,接着用硅胶柱色谱法(仅乙酸乙酯)纯化,以无色油状物的形式得到N-({反-4-[(2,2-二氟乙基)(甲基)氨基]环己基}甲基)-4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基吡啶-2-胺(24mg)。

[0328] 实施例289

[0329] 将{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[顺-2,6-二甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}氨基甲酸叔丁酯(180mg)溶于1,4-二噁烷(1.8mL),添加4M氯化氢/1,4-二噁烷溶液,在室温下搅拌4小时。在反应混合物中添加异丙醚(5mL),滤取生成的固体,用异丙醚洗涤后减压干燥,以白色粉末的形式得到N-[(反-4-氨基环己基)甲基]-4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[顺-2,6-二甲基吗啉-4-基]嘧啶-2-胺二盐酸盐(131mg)。

[0330] 实施例 295

[0331] 将 4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基嘧啶-2-基}氨基)甲基]环己酮(550mg)溶于二氯乙烷(11mL),添加哌嗪-1-羧酸叔丁酯(673mg),搅拌 10 分钟后,添加三乙酰氧基硼氢化钠(766mg),在室温下搅拌 3 小时。加水(50mL),用氯仿(200mL)萃取,用饱和食盐水洗涤。用无水硫酸钠干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=90:10~70:30)纯化,以白色粉末的形式分别得到两种化合物。

[0332] 4-{顺-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基嘧啶-2-基}氨基)甲基]环己基}哌嗪-1-羧酸叔丁酯:472mg,氨基硅胶 TLC(己烷:乙酸乙酯=1:1)中的 Rf 值为 0.42。

[0333] 4-{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基嘧啶-2-基}氨基)甲基]环己基}哌嗪-1-羧酸叔丁酯:290mg,氨基硅胶 TLC(己烷:乙酸乙酯=1:1)中的 Rf 值为 0.30。

[0334] 实施例 325

[0335] 将N-[(反-4-氨基环己基)甲基]-4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基嘧啶-2-胺(250mg)溶于二甲基乙酰胺(2.5mL),添加 2-氟丙基-4-甲基苯磺酸酯(165mg)和碳酸钾(168mg),用微波反应装置在 100℃下搅拌 1 小时,接着在 120℃下搅拌 1.5 小时。加水(10mL),用乙酸乙酯(15mL)萃取后,用饱和食盐水洗涤。用无水硫酸镁干燥有机层,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=40:60)纯化,以白色粉末的形式得到 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2-氟丙基)氨基]环己基}甲基)-6-吗啉-4-基嘧啶-2-胺(183mg)。

[0336] 实施例 326

[0337] 将 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2-氟乙基)氨基]环己基}甲基)-6-吗啉-4-基吡啶-2-胺(50mg)溶于二甲基乙酰胺(500μl),添加磷酸钾(140mg)和 3-溴丙烷-1-醇(26μl),用微波反应装置在 120℃下搅拌 2 小时。加水(10mL),用乙酸乙酯(15mL)萃取后,用饱和食盐水洗涤。用无水硫酸镁干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=60:40)纯化,以白色粉末的形式得到 3-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基吡啶-2-基}氨基)甲基]环己基}(2-氟乙基)氨基]丙烷-1-醇(21mg)。

[0338] 实施例 328

[0339] 将 N-[(反-4-氨基环己基)甲基]-4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基嘧啶-2-胺(100mg)溶于二甲基乙酰胺(1mL),添加 2-氟丙基-4-甲基苯磺酸酯(127mg)和碳酸钾(101mg),用微波反应装置在 160℃下搅拌 1 小时。加水(10mL),用乙酸乙酯(15mL)萃取,用饱和食盐水洗涤。用无水硫酸镁干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=40:60)纯化,以白色粉末的形式得到 3-{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基嘧啶-2-基}氨基)甲基]环己基}-5-甲基-1,3-噁唑烷-2-酮(39mg)。

[0340] 实施例 333

[0341] 将 N-[(反-4-氨基环己基)甲基]-4-[2-(二氟甲基)-1H-苯并咪

唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 胺 (50mg) 溶于二甲基乙酰胺 (500μl)，添加 2- 氟丙基 -4- 甲基苯磺酸酯 (63mg) 和磷酸钾 (103mg)，用微波反应装置在 200℃下搅拌 1 小时。加水 (10mL)，用乙酸乙酯 (15mL) 萃取后，用饱和食盐水洗涤。用无水硫酸镁干燥有机层，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 40 ： 60) 纯化，以白色粉末的形式得到 N-({ 反 -4-[双 (2- 氟丙基) 氨基] 环己基 } 甲基)-4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 胺 (8mg)。

[0342] 实施例 335

[0343] 将 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-({ 反 -4-[(2- 氟 -1- 甲基乙基) 氨基] 环己基 } 甲基)-6- 吗啉 -4- 基嘧啶 -2- 胺 (150mg) 溶于二甲基乙酰胺 (1.5mL)，添加碳酸钾 (120mg) 和水 (5μl)，用微波反应装置在 160℃下搅拌 2 小时，在 180℃下搅拌 3 小时。加水 (10mL)，用乙酸乙酯 (15mL) 萃取后，用饱和食盐水洗涤。用无水硫酸镁干燥有机层，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 40 ： 60) 纯化，接着用硅胶柱色谱法 (己烷：乙酸乙酯＝ 20 ： 80) 纯化，以白色粉末的形式得到 3-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 氨基) 甲基] 环己基 }-4- 甲基 -1,3- 噁唑烷 -2- 酮 (66mg)。

[0344] 实施例 343

[0345] 将 N-[(反 -4- 氨基环己基) 甲基]-4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 胺 (200mg) 溶于乙醇 (4mL)，添加 2-(氟甲基) 环氧乙烷 (34μl) 和二异丙基乙胺 (99μl)，在 80℃下搅拌 6 小时。加水 (10mL)，用乙酸乙酯 (15mL) 萃取后，用饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 40 ： 60) 纯化，以白色粉末的形式得到 1-({ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 氨基)-3- 氟丙烷 -2- 醇 (128mg)。

[0346] 实施例 345

[0347] 将 1-({ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 氨基)-3- 氟丙烷 -2- 醇 (100mg) 溶于二甲基乙酰胺 (2mL)，添加碳酸二乙酯 (34μl) 和甲醇钠 (30mg)，在室温下搅拌 2 小时。加水 (10mL)，用乙酸乙酯 (15mL) 萃取后，用饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 40 ： 60) 纯化，以白色粉末的形式得到 3-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 }-5-(氟甲基)-1,3- 噁唑烷 -2- 酮 (50mg)。

[0348] 实施例 353

[0349] 将 1-({ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 氨基)-3- 丁烷 -2- 醇 (40mg) 溶于四氢呋喃 (800μl)，添加羰基二咪唑 (73mg) 和三乙胺 (32μl)，在室温下搅拌 3 小时。加水 (10mL)，用乙酸乙酯 (15mL) 萃取后，用饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 40 ： 60) 纯化，以白色粉末的形式得到 3-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 }-5-(乙基)-1,3- 噁唑烷 -2- 酮 (32mg)。

[0350] 实施例 386

[0351] 将 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-({反-4-[(2-氟-1-甲基乙基)氨基]环己基}甲基)-6-吗啉-4-基嘧啶-2-胺(100mg)溶于二氯甲烷(1.5mL),添加 1,4-二噁烷-2,5-二醇(28mg)和三乙酰氧基硼氢化钠(61mg),在室温下搅拌 3 小时。加水(10mL),用氯仿(15mL)萃取。用无水硫酸钠干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=60:40)纯化,以白色粉末的形式得到 2-[{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-(吗啉-4-基)嘧啶-2-基}氨基)甲基]环己基}(1-氟丙烷-2-基)氨基]乙醇(80mg)。

[0352] 实施例 417

[0353] 将反-N-{4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-基}环己烷-1,4-二胺(100mg)溶于乙醇(2mL),添加 1H-1,2,3-苯并三唑-1-基甲醇(17mg),在室温下搅拌 5 小时后,在反应混合物中添加四氢硼酸钠(170mg),在室温下搅拌 1 小时。添加饱和碳酸氢钠水溶液(100mL),用乙酸乙酯(100mL)萃取,用饱和食盐水(100mL)洗涤。用无水硫酸镁干燥有机层,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=50:50～0:100)、氯仿:甲醇(100:0～98:2)纯化,得到游离体(35mg)。

[0354] 将游离体溶于二噁烷(2mL),添加 4M 氯化氢/1,4-二噁烷溶液(55μL),再添加异丙醚(5mL),滤取析出的固体后,用异丙醚洗涤,以白色粉末的形式得到反-N′-{4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3R)-3-甲基吗啉-4-基]嘧啶-2-基}-N,N-二甲基环己烷-1,4-二胺二盐酸盐(31mg)。

[0355] 实施例 433

[0356] 将 1-{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-(吗啉-4-基)嘧啶-2-基}氨基)甲基]环己基}氮杂环丁烷-3-醇(55mg)溶于二氯乙烷(550μl),添加双(2-甲氧基乙基)氨基三氟化硫(21μl),在 0℃下搅拌 2 小时,在室温下搅拌 3 小时。加水(10mL),用乙酸乙酯(15mL)萃取后,用饱和食盐水洗涤。用无水硫酸镁干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(己烷:乙酸乙酯=60:40)纯化,以白色粉末的形式得到 4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-N-{[反-4-(3-氟氮杂环丁烷-1-基)环己基]甲基}-6-(吗啉-4-基)嘧啶-2-胺(8.7mg)。

[0357] 实施例 436

[0358] 将 N-[(反-4-氨基环己基)甲基]-4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-吗啉-4-基嘧啶-2-胺(100mg)溶于氯仿(2mL),添加 1-氯-2-异氰酸根合乙烷(1-クロロ-2-イソシアネートエタン)(21μl)和碳酸钾(76mg),在室温下搅拌 1 小时。确认脲形成的进行后,在加热回流下搅拌 6 小时。加水(10mL),用乙酸乙酯(15mL)萃取,用饱和食盐水洗涤。用无水硫酸镁干燥有机层后,减压蒸除溶剂。将残渣用氨基硅胶柱色谱法(乙酸乙酯)纯化,以白色粉末的形式得到 1-{反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-(吗啉-4-基)嘧啶-2-基}氨基)甲基]环己基}咪唑烷-2-酮(35mg)。

[0359] 实施例 439

[0360] 将 1-({反-4-[({4-[2-(二氟甲基)-1H-苯并咪唑-1-基]-6-[(3S)-3-甲基吗啉-4-基]嘧啶-2-基}氨基)甲基]环己基}氨基)-2-甲基丙烷-2-醇(100mg)溶于乙

醇 (2mL)，添加三乙胺 (31μl) 和 1H- 苯并三唑 -1- 基甲醇 (82mg)，在室温下搅拌 2 小时。在反应混合物中添加硼氢化锂 (4.8mg)，进一步在室温下搅拌 1 小时。加水 (10mL)，用乙酸乙酯 (15mL) 萃取，用饱和食盐水洗涤。用无水硫酸镁干燥有机层后，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 70 ： 30) 纯化，以白色粉末的形式得到 4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-N-{[反 -4-(5,5- 二甲基 -1,3- 噁唑烷 -3- 基) 环己基] 甲基 }-6-[(3S)-3- 甲基吗啉 -4- 基] 嘧啶 -2- 胺 (68mg)。

[0361] 实施例 540

[0362] 将 1-({ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 氨基)-2- 甲基丙烷 -2- 醇 (100mg) 溶于二甲基乙酰胺 (2mL)，添加氯乙酰氯 (36μl) 和叔丁醇钾 (102mg)，在室温下搅拌 20 小时。添加饱和食盐水 (10mL)，用乙酸乙酯 (15mL) 萃取。用无水硫酸钠干燥有机层，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 60 ： 40) 纯化，以白色粉末的形式得到 4-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 }-6,6- 二甲基吗啉 -3- 酮 (35mg)。

[0363] 实施例 542

[0364] 将 1-({ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 氨基)-2- 甲基丙烷 -2- 醇 (100mg) 溶于二甲基乙酰胺 (2mL)，添加溴乙酸甲酯 (22μl) 和三乙胺 (35μl)，用微波反应装置在 180℃下搅拌 3 小时。接着，添加 4- 甲基苯磺酸 (78mg)，用微波反应装置在 100℃下搅拌 30 分钟。添加饱和碳酸氢钠水溶液 (10mL) 使水层呈碱性后，用乙酸乙酯 (15mL) 萃取。用无水硫酸钠干燥有机层后，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 60 ： 40) 纯化，以淡黄色粉末的形式得到 4-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 }-6,6- 二甲基吗啉 -2- 酮 (20mg)。

[0365] 实施例 554

[0366] 将 N-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 甘氨酸甲酯 (80mg) 溶于四氢呋喃 (1.6mL)，在冰冷下添加催化剂量的氯化锌 (II)(2mg) 和乙基溴化镁 (1.06M 四氢呋喃溶液，428μl)，在 0℃下搅拌 1 小时。在反应混合物中添加饱和食盐水 (10mL)，用乙酸乙酯 (15mL) 萃取。用无水硫酸镁干燥有机层后，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 40 ： 60) 纯化，以白色粉末的形式得到 3-[({ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 氨基) 甲基] 戊烷 -3- 醇 (17mg)。

[0367] 实施例 555

[0368] 将 1-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 哌啶 -3- 基乙酸酯 (50mg) 溶于甲醇 (500μl)，添加碳酸钾 (36mg) 和水 (5μl)，在加热回流下搅拌 2 小时。在反应混合物中添加饱和食盐水 (10mL)，用乙酸乙酯 (15mL) 萃取。用无水硫酸镁干燥有机层后，减压蒸除溶剂。将残渣用氨基硅胶柱色谱法 (己烷：乙酸乙酯＝ 40 ： 60) 纯化，以白色粉末的形式得到 1-{ 反 -4-[({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6-(吗啉 -4- 基) 嘧啶 -2- 基 } 氨基) 甲基] 环己基 } 哌

啶 -3- 醇 (26mg)。

[0369] 实施例 570

[0370] 将反 -N-{6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基} 环己烷 -1,4- 二胺 (100mg) 溶于二氯甲烷 (1mL),在冰冷下添加三乙胺 (47μl) 和 2,4- 二溴丁酰氯 (45μl),在 0℃下搅拌 1 小时。在反应混合物中加水 (30mL),用乙酸乙酯 (30mL) 萃取,用饱和食盐水洗涤。用无水硫酸镁干燥有机层,减压蒸除溶剂。将残渣用硅胶柱色谱法 (己烷 : 乙酸乙酯 = 70 : 30 ～ 50 : 50) 纯化,得到对应的酰基化体 (80mg 19%)。将所得的酰基化体溶于四氢呋喃 (1mL),添加叔丁醇钾 (15mg),在室温下搅拌 1 小时。在反应混合物中加水 (30mL),用乙酸乙酯 (30mL) 萃取,用饱和食盐水洗涤。用无水硫酸镁干燥有机层,减压蒸除溶剂。将残渣用硅胶柱色谱法 (己烷 : 乙酸乙酯 = 50 : 50 ～ 0 : 100) 纯化,以淡黄色粉末的形式得到 3- 溴 -1-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2-(吗啉 -4- 基) 嘧啶 -4- 基} 氨基) 环己基] 吡咯烷 -2- 酮 (60mg)。

[0371] 实施例 A1

[0372] 在室温下在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基} 环己烷 -1,4- 二胺 (11.1mg)、丙酸 (1.9mg)、1- 羟基苯并三唑 (3.4mg) 及三乙胺 (3.5μL) 的 N,N- 二甲基甲酰胺 (1.0mL) 溶液中添加 PS- 碳二亚胺 (PS-Carbodiimide : Biotage 公司)(100mg),搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde :Biotage 公司)(50mg) 及 MP- 碳酸酯 (MP-Carbonate :Biotage 公司) (50mg),搅拌 4 小时,滤去不溶物。将滤液减压浓缩,得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基} 氨基) 环己基] 丙酰胺 (9.4mg)。

[0373] 这里,为了求出 RT 而进行的 HPLC 的条件如下所示。

[0374] 柱 :Wakosil-II 5C18AR(和光纯药)(粒径 :5μm,内径 :2.0mm,长度 :30mm)

[0375] 流动相 :A 液 5mM 三氟乙酸水溶液、B 液 甲醇

[0376] 流速 :1.2mL/min ;检测波长 :254nm ;柱温 :35.0℃ ;注入量 :5μL

[0377] [表 4]

[0378]

时间 (min)	A 液 (%)	B 液 (%)	洗脱
0-4	95 → 0	5 → 100	梯度
4-4.5	0	100	等度

[0379] 实施例 B1

[0380] 相对于乙磺酰氯 (3.9mg),添加反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基} 环己烷 -1,4- 二胺 (11.1mg) 及三乙胺 (8.4μL) 的二氯甲烷 (0.5mL) 溶液,在室温下搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde :Biotage 公司)(50mg)、PS- 缓血酸胺 (PS-Trisamine : Biotage 公司)(50mg) 及二氯甲烷 (1.0mL),搅拌 4 小时,滤去不溶物。将滤液减压浓缩,通过 HPLC 对残渣进行分离纯化,得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪

唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 氨基) 环己基] 乙磺胺 (8.0mg)。

[0381] 这里,为了求出 RT 而进行的 HPLC 的条件如下所示。

[0382] 柱 :ACQUITY UPLC HSS T3(,粒径 :1.8μm,内径 :2.1mm,长度 :50mm)

[0383] 流动相 :A 液 0.1%甲酸水溶液、B 液 0.1%甲酸 - 甲醇溶液

[0384] 流速 :0.70mL/min ;检测波长 :254nm ;柱温 :40.0℃ ;注入量 :2μL

[0385] [表 5]

[0386]

时间 (min)	A 液 (%)	B 液 (%)	洗脱
0-3	95 → 10	5 → 90	梯度
3-4	10	90	等度

[0387] 实施例 C1

[0388] 在室温下在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 } 环己烷 -1,4- 二胺 (11.1mg) 及乙醛 (1.1mg) 的 N,N- 二甲基甲酰胺 (0.3mL)/ 乙酸 (0.03mL) 溶液中添加 MP- 三乙酰氧基硼氢化物 (MP-Triacetoxyborohydride :Biotage 公司)(75mg),搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde :Biotage 公司)(50mg) 及 N,N- 二甲基甲酰胺 (0.3mL),搅拌 4 小时,通过使用 BondElut(注册商标)SCX(洗脱液 :浓氨水 / 甲醇 = 1/9) 的固相萃取进行纯化。将滤液减压浓缩后,通过 HPLC 对残渣进行分离纯化,得到反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基 -1,3,5- 三嗪 -2- 基 }-N' - 乙基环己烷 -1,4- 二胺 (0.6mg)。

[0389] 为了求出 RT 而进行的 HPLC 的条件同实施例 B1。

[0390] 实施例 D1

[0391] 在室温下在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 环己烷 -1,4- 二胺 (11.1mg)、丙酸 (1.9mg)、1- 羟基苯并三唑 (3.4mg) 及三乙胺 (3.5μL) 的 N,N- 二甲基甲酰胺 (1.0mL) 溶液中添加 PS- 碳二亚胺 (PS-Carbodiimide : Biotage 公司)(100mg),搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde :Biotage 公司)(50mg) 及 MP- 碳酸酯 (MP-Carbonate :Biotage 公司)(50mg),搅拌 4 小时,滤去不溶物。将滤液减压浓缩,得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 氨基) 环己基] 丙酰胺 (6.7mg)。

[0392] 为了求出 RT 而进行的 HPLC 的条件同实施例 B1。

[0393] 实施例 E1

[0394] 相对于甲磺酰氯 (3.4mg),添加反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 环己烷 -1,4- 二胺 (11.1mg) 及三乙胺 (8.4μL) 的二氯甲烷 (0.5mL) 溶液,在室温下搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde :Biotage 公司)(50mg)、PS- 缓血酸胺 (PS-Trisamine :Biotage 公司)(50mg) 及二氯甲烷 (1.0mL),搅拌 4 小时,滤去不溶物。将滤液减压浓缩后,通过 HPLC 对残渣进行分离纯化,得到 N-[反 -4-({4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基

嘧啶 -2- 基 } 氨基) 环己基] 甲磺酰胺 (6.5mg)。

[0395] 为了求出 RT 而进行的 HPLC 的条件同实施例 B1。

[0396] 实施例 F1

[0397] 在室温下在反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 } 环己烷 -1,4- 二胺 (11.1mg) 及乙醛 (1.1mg) 的 N,N- 二甲基甲酰胺 (0.3mL)/ 乙酸 (0.03mL) 溶液中添加 MP- 三乙酰氧基硼氢化物 (MP-Triacetoxyborohydride :Biotage 公司)(75mg),搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde : Biotage 公司)(50mg) 及 N,N- 二甲基甲酰胺 (0.3mL),搅拌 4 小时,通过使用 BondElut(注册商标)SCX(洗脱液 :浓氨水 / 甲醇 = 1/9) 的固相萃取进行纯化。将滤液减压浓缩后,通过 HPLC 对残渣进行分离纯化,得到反 -N-{4-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-6- 吗啉 -4- 基嘧啶 -2- 基 }-N' - 乙基环己烷 -1,4- 二胺 (0.5mg)。

[0398] 为了求出 RT 而进行的 HPLC 的条件同实施例 B1。

[0399] 实施例 G1

[0400] 在室温下在反 -N-{6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 环己烷 -1,4- 二胺 (11.1mg)、丙酸 (1.9mg)、1- 羟基苯并三唑 (3.4mg) 及三乙胺 (6.9μL) 的 N,N- 二甲基甲酰胺 (1.0mL) 溶液中添加 PS- 碳二亚胺 (PS-Carbodiimide : Biotage 公司)(100mg),搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde :Biotage 公司)(50mg) 及 MP- 碳酸酯 (MP-Carbonate :Biotage 公司) (50mg),搅拌 4 小时,滤去不溶物。将滤液减压浓缩后,通过 HPLC 对残渣进行分离纯化,得到 N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基] 丙酰胺 (7.4mg)。

[0401] 为了求出 RT 而进行的 HPLC 的条件同实施例 B1。

[0402] 实施例 H1

[0403] 相对于 3,3,3- 三氟丙烷 -1- 磺酰氯 (5.9mg),添加反 -N-{6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 环己烷 -1,4- 二胺 (11.1mg) 及三乙胺 (8.4μL) 的二氯甲烷 (0.5mL) 溶液,在室温下搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde :Biotage 公司)(50mg)、PS- 缓血酸胺 (PS-Trisamine : Biotage 公司)(50mg) 及二氯甲烷 (1.0mL),搅拌 4 小时,滤去不溶物。将滤液减压浓缩后,通过 HPLC 对残渣进行分离纯化,得到 N-[反 -4-({6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 氨基) 环己基]-3,3,3- 三氟丙烷 -1- 磺胺 (8.9mg)。

[0404] 为了求出 RT 而进行的 HPLC 的条件同实施例 B1。

[0405] 实施例 J1

[0406] 在室温下在反 -N-{6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗啉 -4- 基嘧啶 -4- 基 } 环己烷 -1,4- 二胺 (11.1mg) 及乙醛 (1.1mg) 的 N,N- 二甲基甲酰胺 (0.3mL)/ 乙酸 (0.03mL) 溶液中添加 MP- 三乙酰氧基硼氢化物 (MP-Triacetoxyborohydride :Biotage 公司)(75mg),搅拌过夜。在室温下在反应混合物中添加 PS- 苯甲醛 (PS-Benzaldehyde : Biotage 公司)(50mg) 及 N,N- 二甲基甲酰胺 (0.3mL),搅拌 4 小时,通过使用 BondElut(注册商标)SCX(洗脱液 :浓氨水 / 甲醇 = 1/9) 的固相萃取进行纯化。将滤液减压浓缩后,通过 HPLC 对残渣进行分离纯化,得到反 -N-{6-[2-(二氟甲基)-1H- 苯并咪唑 -1- 基]-2- 吗

啉 -4- 基嘧啶 -4- 基 }-N' - 乙基环己烷 -1,4- 二胺 (0.3mg)。

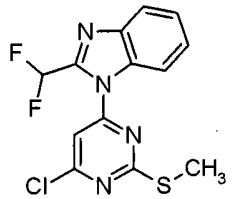
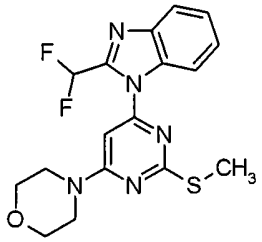
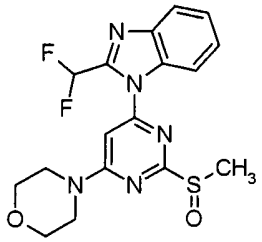
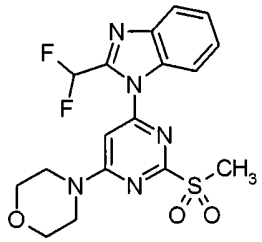
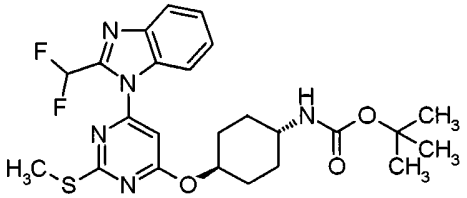
[0407] 为了求出 RT 而进行的 HPLC 的条件同实施例 B1。

[0408] 各实施例化合物的结构示于表 17 ～ 88,制造方法及物理化学数据示于表 89 ～ 129。与实施例 A1 ～ J1 的方法同样地制得的各实施例化合物的结构示于表 130 ～ 165,物理化学数据示于表 166 ～ 172。

[0409] 物理化学数据的 Syn 栏中存在 2 个以上的编号时,是指按照编号的记载顺序来制造。

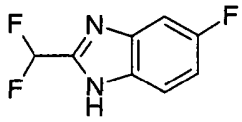
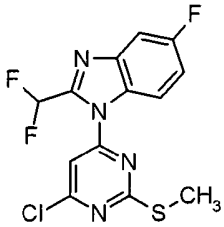
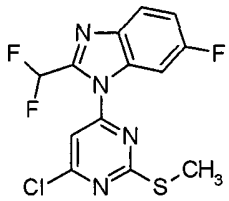
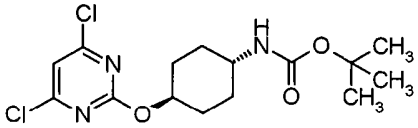
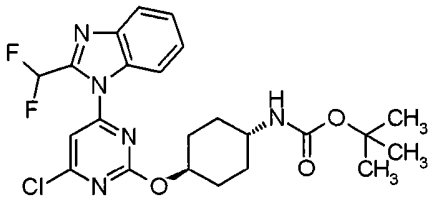
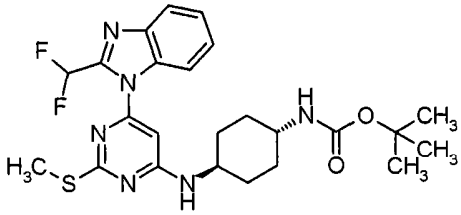
[0410] [表 6]

[0411]

PEx	PSyn	Str	DATA
1	1		ESI+: 327
2	2		ESI+: 378
3	3		ESI+: 394
4	4		ESI+: 410
5	5		ESI+: 528 [M+Na]

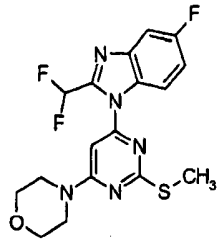
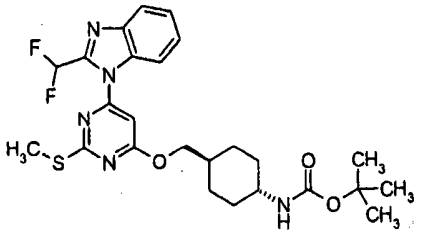
[0412] [表 7]

[0413]

PEx	PSyn	Str	DATA
6	6		ESI+: 187
7-1	7		ESI+: 345
7-2	7		ESI+: 345
8	8		ESI+: 384 [M+Na]
9	1		ESI+: 516 [M+Na]
10	2		ESI+: 527 [M+Na]

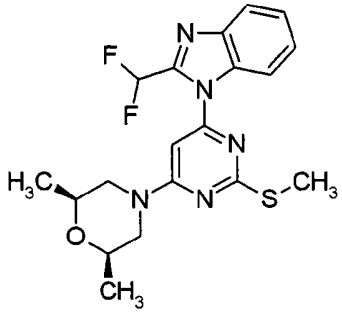
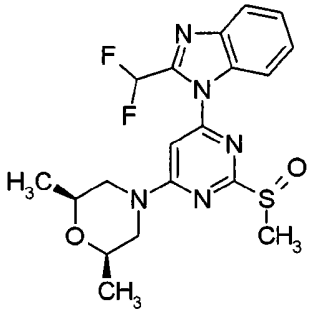
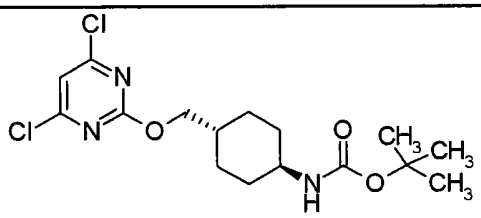
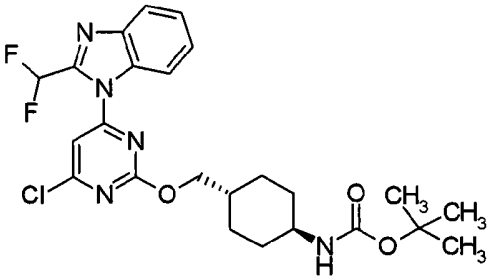
[0414] [表 8]

[0415]

PEx	PSyn	Str	DATA
11	2		ESI+: 396
12	2		ESI+: 396
13	5		ESI+: 542 [M+Na]

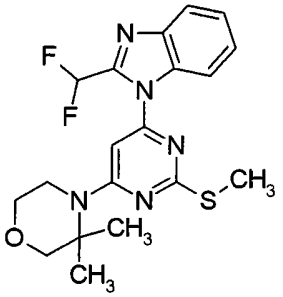
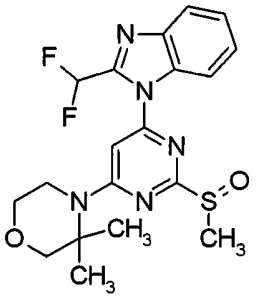
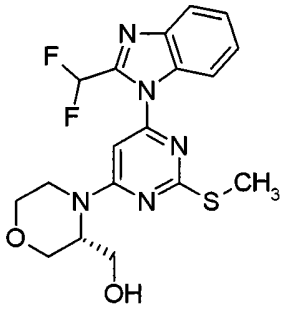
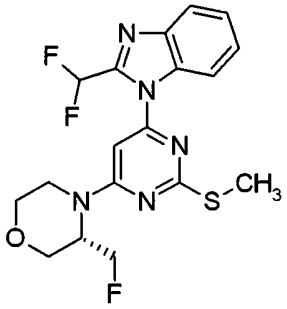
[0416] [表 9]

[0417]

PEx	PSyn	Str	DATA
14	2		ESI+: 406
15	3		ESI+: 422
16	16		ESI+: 398 [M+Na]
17	1		ESI+: 530 [M+Na]

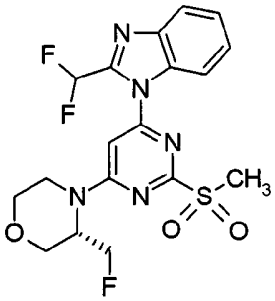
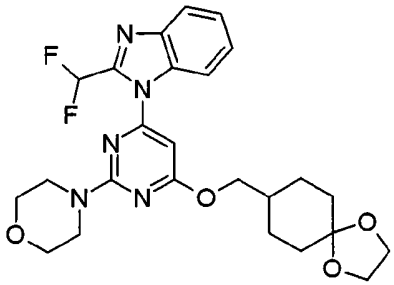
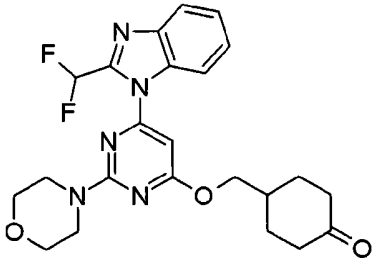
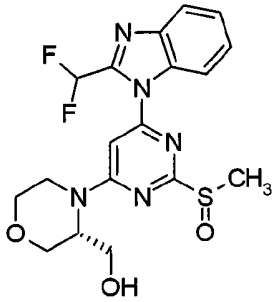
[0418] [表 10]

[0419]

PEx	PSyn	Str	
18	2		ESI+: 406
19	3		ESI+: 422
20	2		ESI+: 408
21	2		ESI+: 410

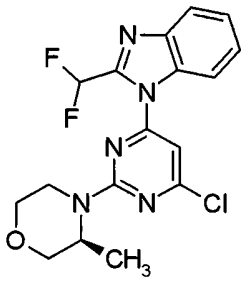
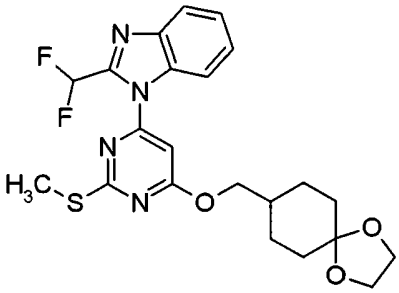
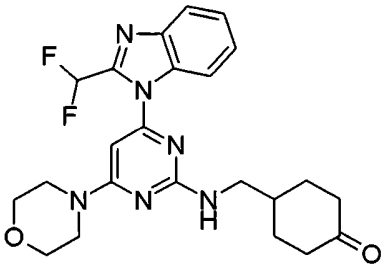
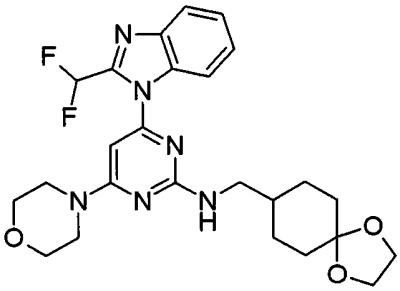
[0420] [表 11]

[0421]

PEx	PSyn	Str	DATA
22	4		ESI+: 442
23	23		ESI+: 502
24	24		ESI+: 458
25	3		ESI+: 424

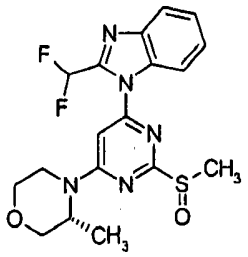
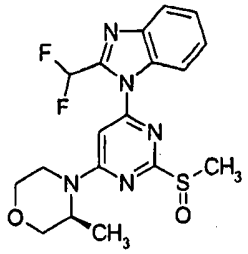
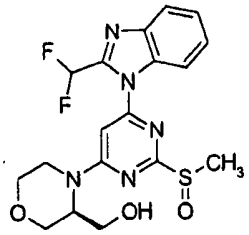
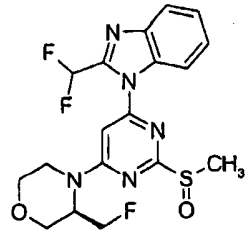
[0422] [表 12]

[0423]

PEx	PSyn	Str	DATA
26	1		ESI+: 380
27	5		ESI+: 463
28	24		ESI+: 479 [M+Na]
29	1		ESI+: 523 [M+Na]

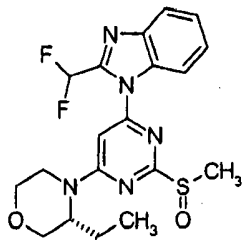
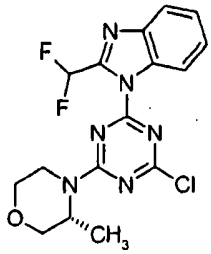
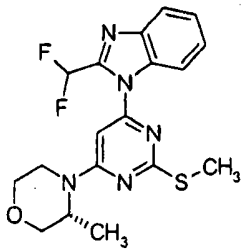
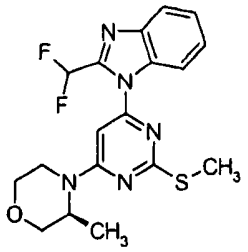
[0424] [表 13]

[0425]

PEx	PSyn	Str	DATA
30	3		ESI+: 408
31	3		ESI+: 408
32	3		ESI+: 424
33	3		ESI+: 426

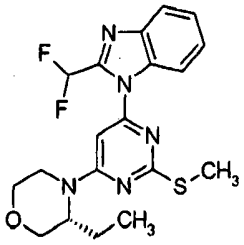
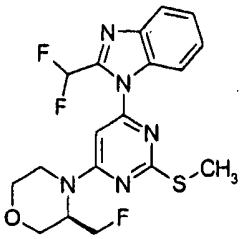
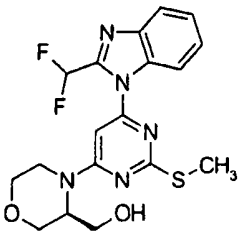
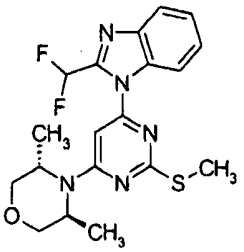
[0426] [表 14]

[0427]

PEx	PSyn	Str	DATA
34	3		ESI+: 422
35	1		ESI+: 381
36	2		ESI+: 392
37	2		ESI+: 392

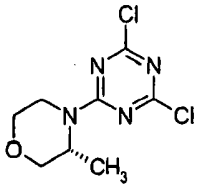
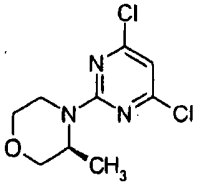
[0428] [表 15]

[0429]

PEx	PSyn	Str	DATA
38	2		ESI+: 406
39	2		ESI+: 410
40	2		ESI+: 408
41	2		ESI+: 406

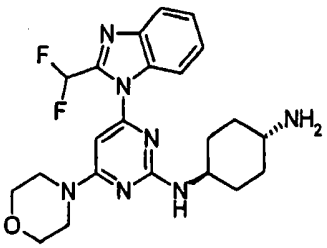
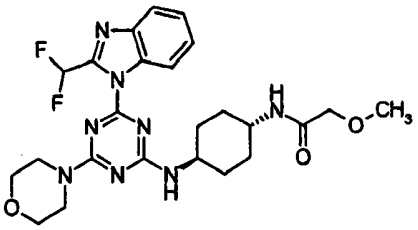
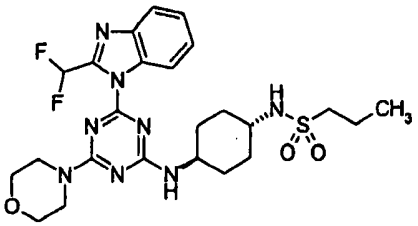
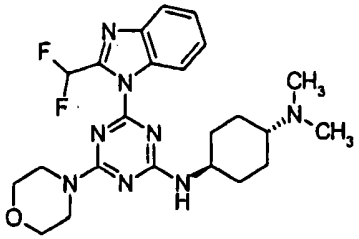
[0430] [表 16]

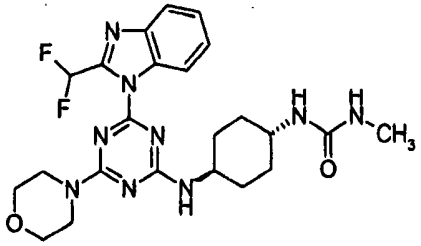
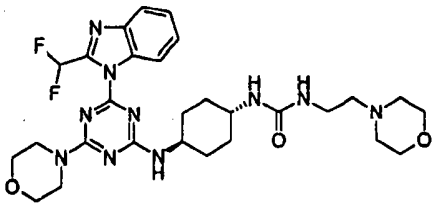
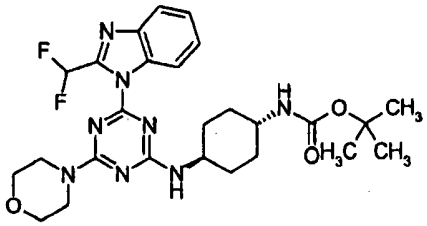
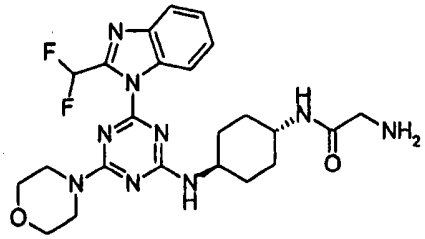
[0431]

PEx	PSyn	Str	DATA
42	2		ESI+: 249
43	2		ESI+: 248

[0432] [表 17]

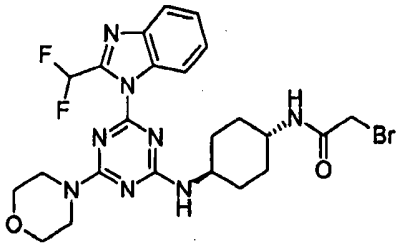
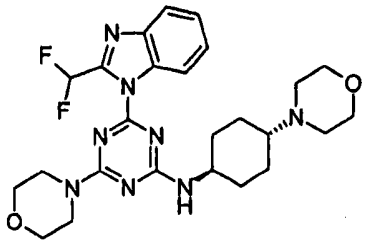
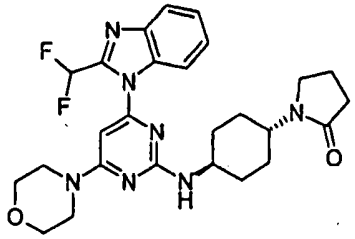
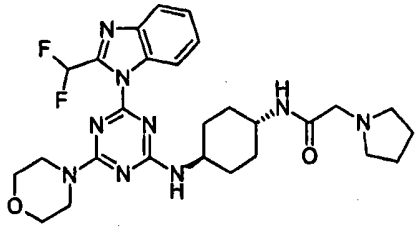
[0433]

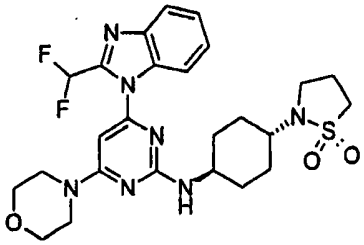
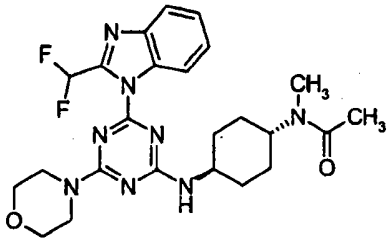
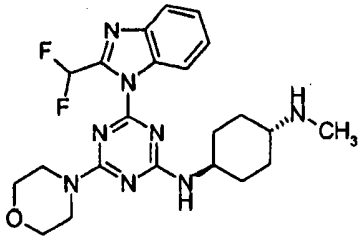
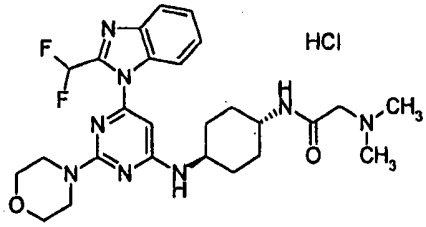
Ex	Str
1	
2	
3	
4	

Ex	Str
5	
6	
7	
8	

[0434] [表 18]

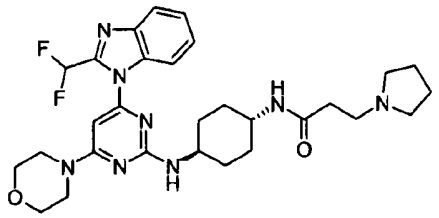
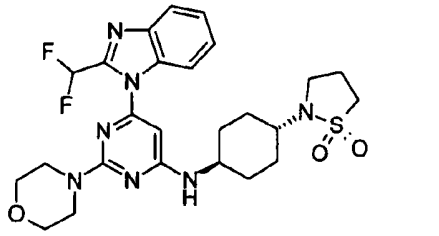
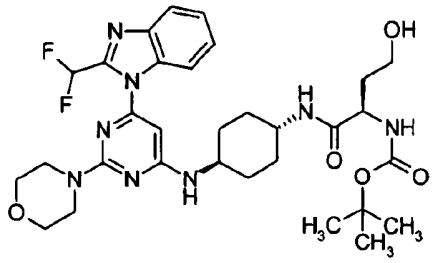
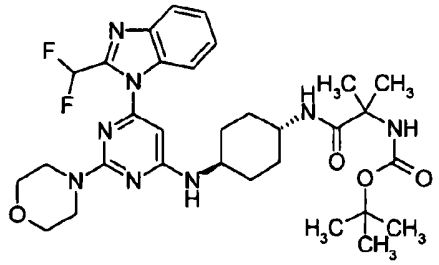
[0435]

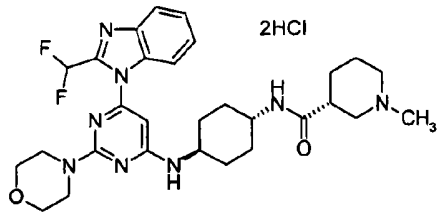
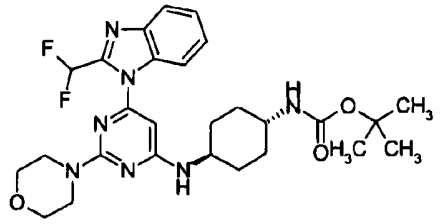
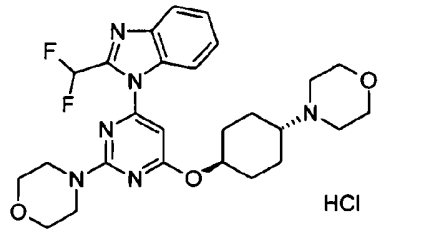
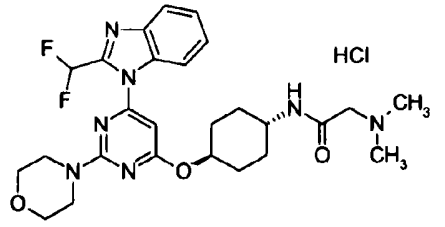
Ex	Str
9	
10	
11	
12	

Ex	Str
13	
14	
15	
16	

[0436] [表 19]

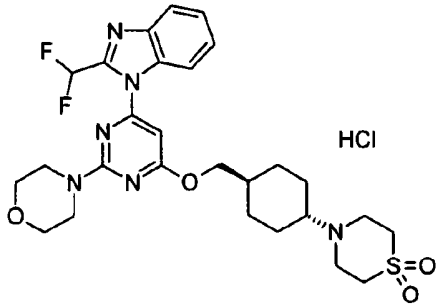
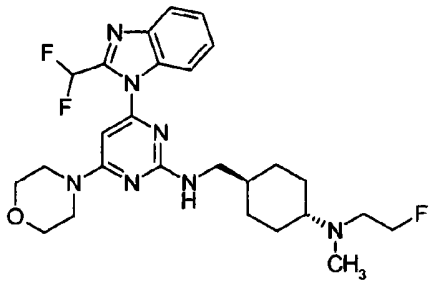
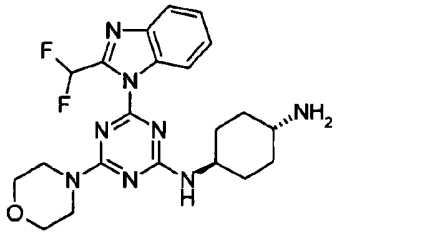
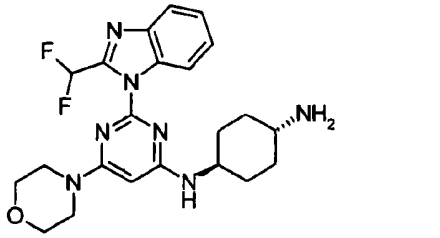
[0437]

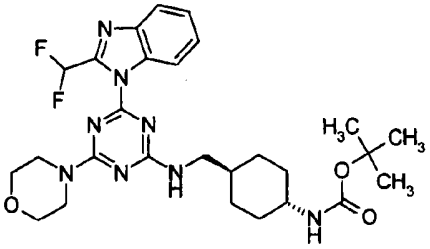
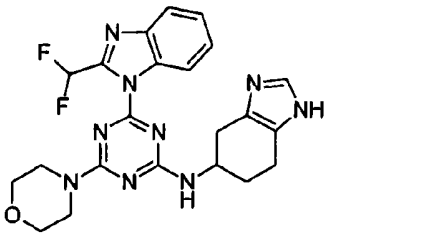
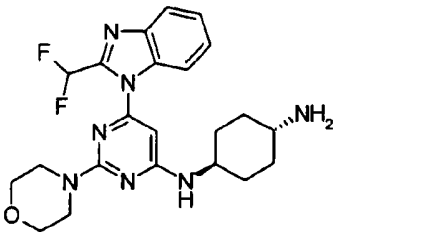
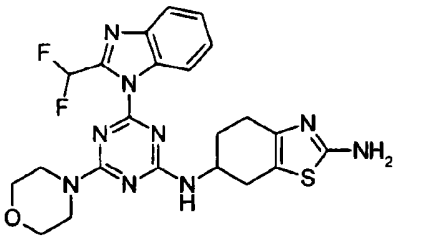
Ex	Str
17	
18	
19	
20	

Ex	Str
21	
22	
23	
24	

[0438] [表 20]

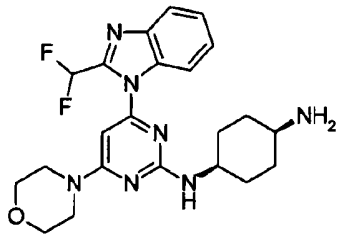
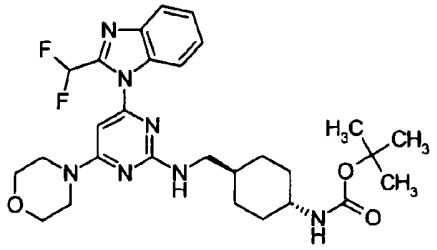
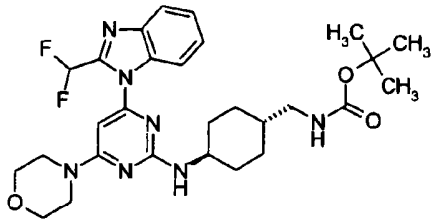
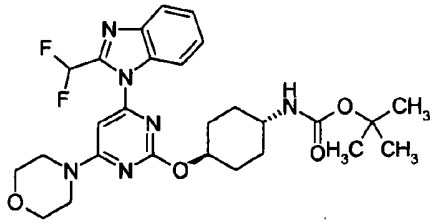
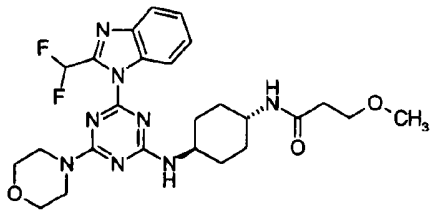
[0439]

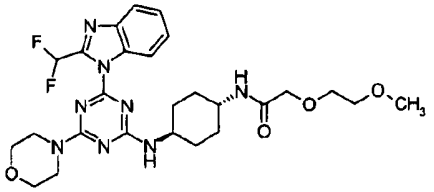
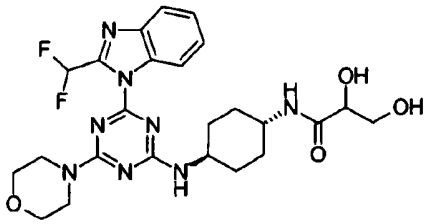
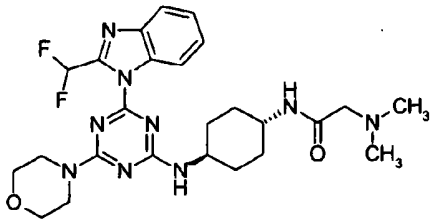
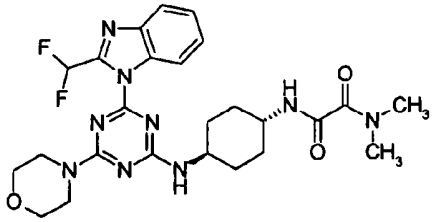
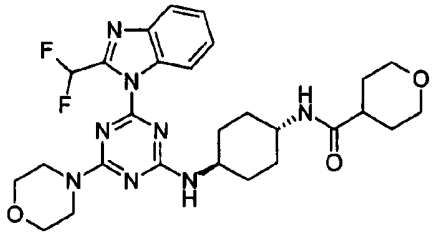
Ex	Str
25	
26	
27	
28	

Ex	Str
29	
30	
31	
32	

[0440] [表 21]

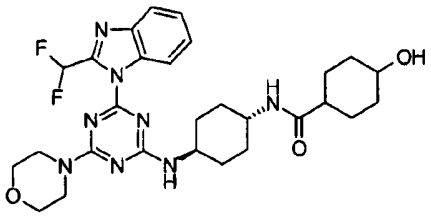
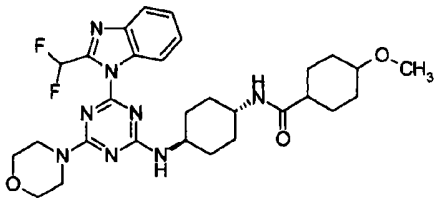
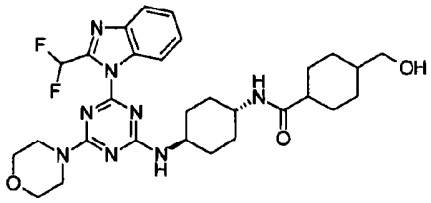
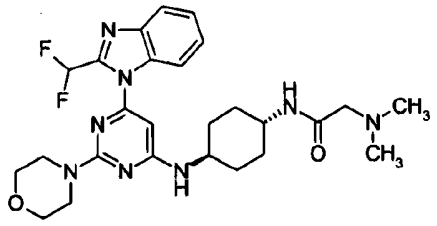
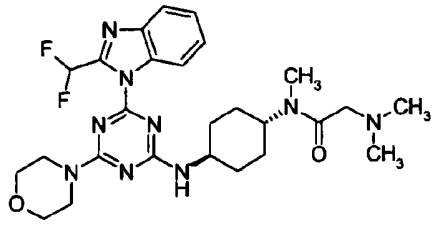
[0441]

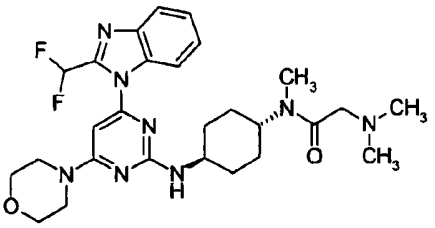
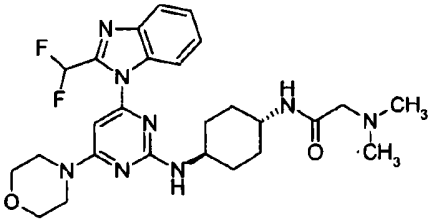
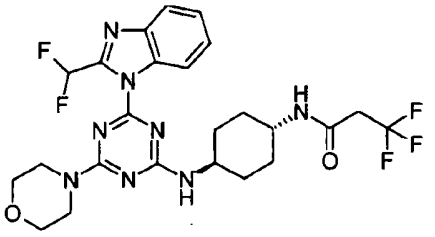
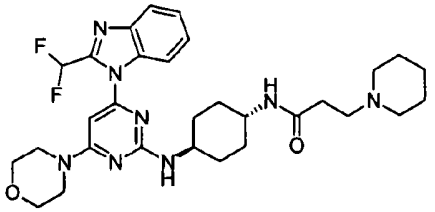
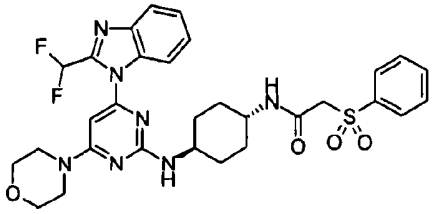
Ex	Str
33	
34	
35	
36	
37	

Ex	Str
38	
39	
40	
41	
42	

[0442] [表 22]

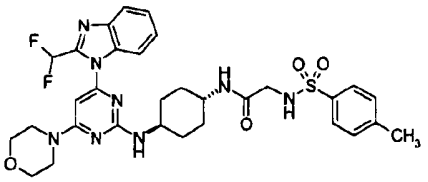
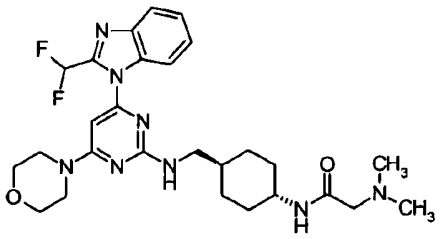
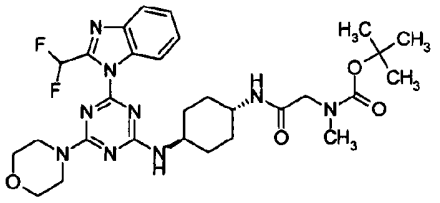
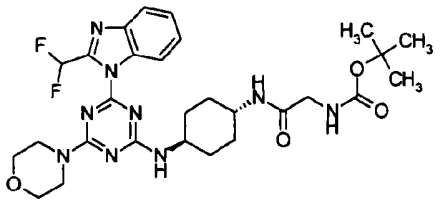
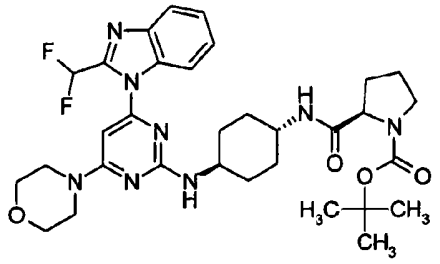
[0443]

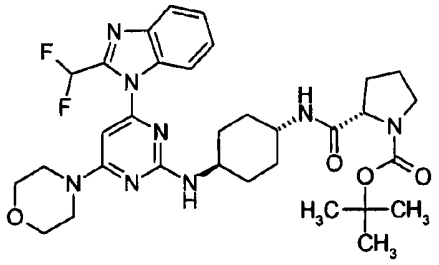
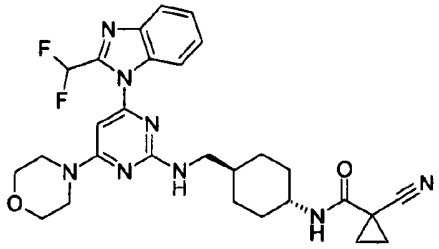
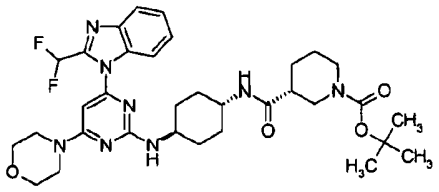
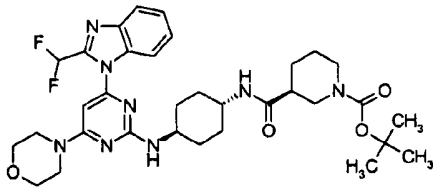
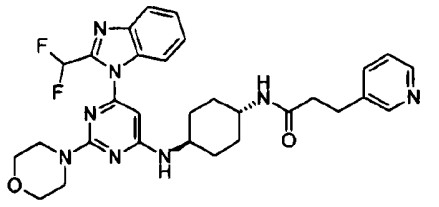
Ex	Str
43	
44	
45	
46	
47	

Ex	Str
48	
49	
50	
51	
52	

[0444] [表 23]

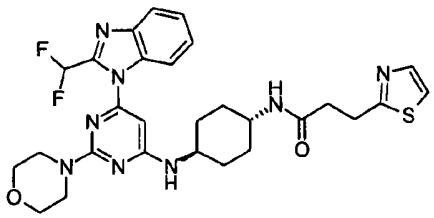
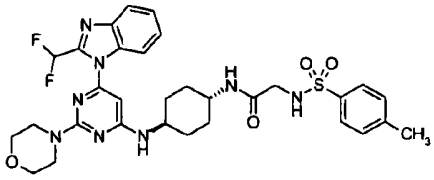
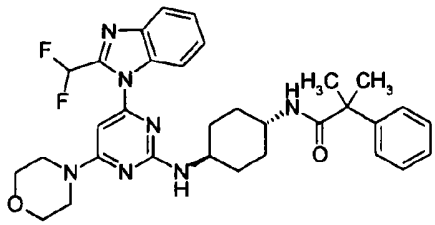
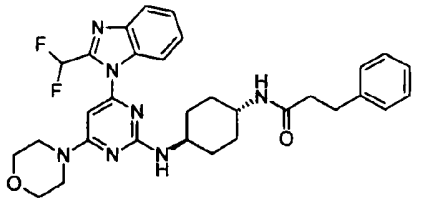
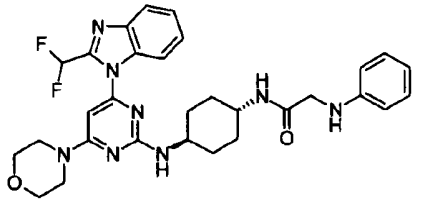
[0445]

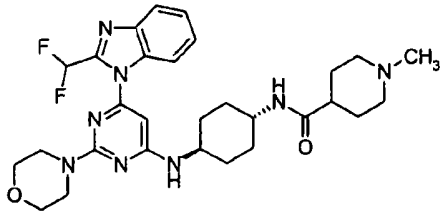
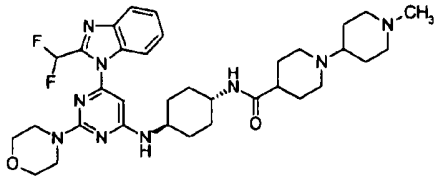
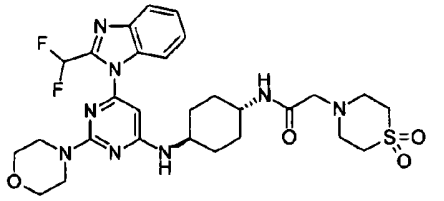
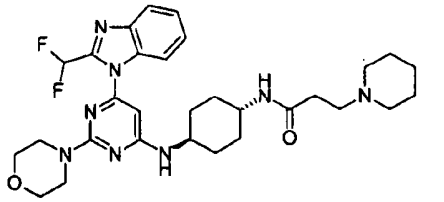
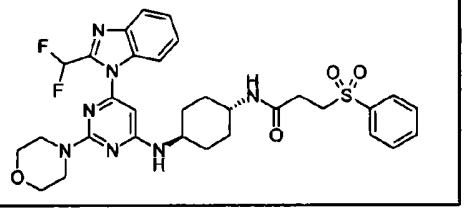
Ex	Str
53	
54	
55	
56	
57	

Ex	Str
58	
59	
60	
61	
62	

[0446] [表 24]

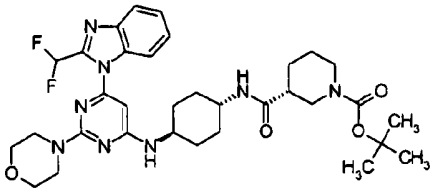
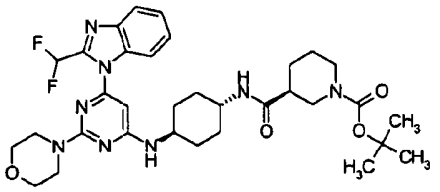
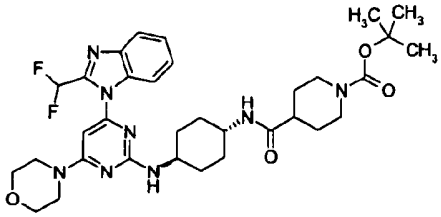
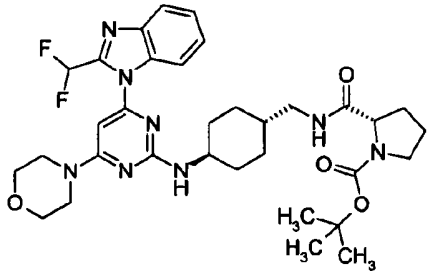
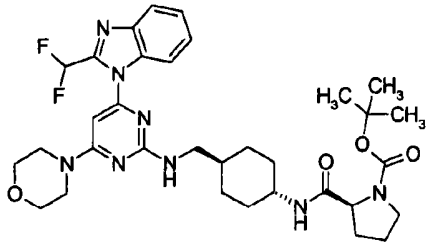
[0447]

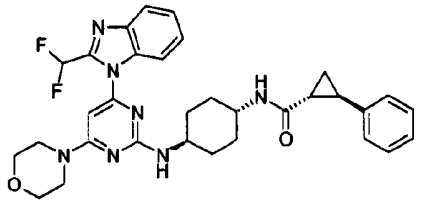
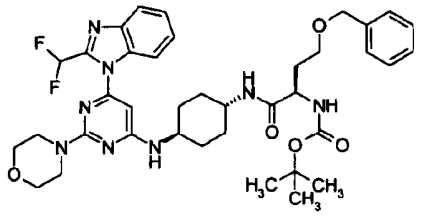
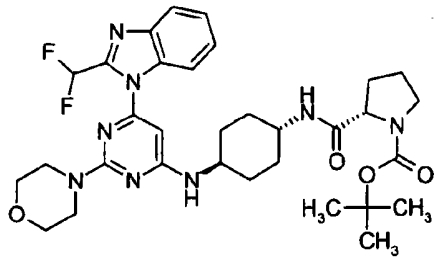
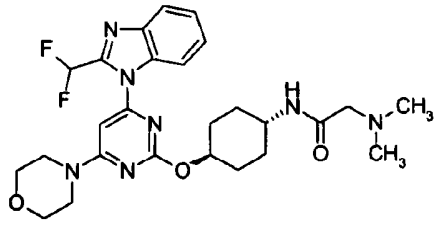
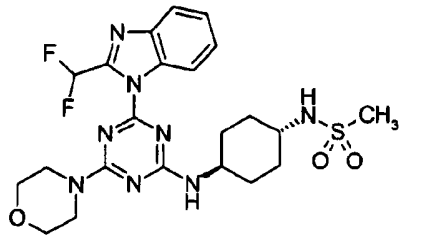
Ex	Str
63	
64	
65	
66	
67	

Ex	Str
68	
69	
70	
71	
72	

[0448] [表 25]

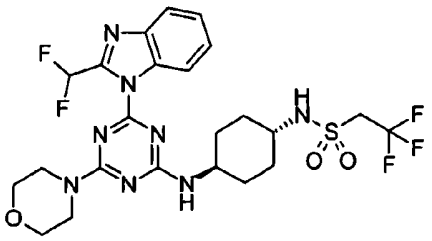
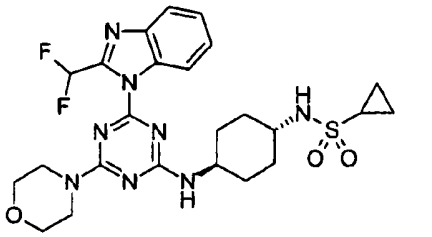
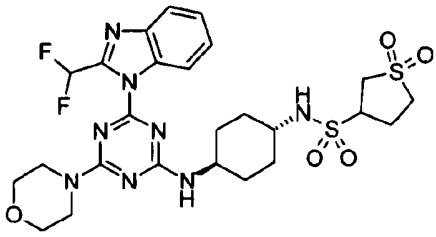
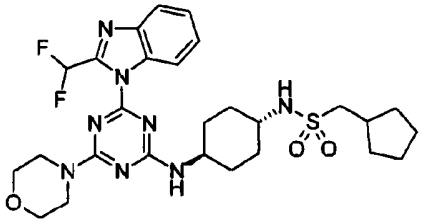
[0449]

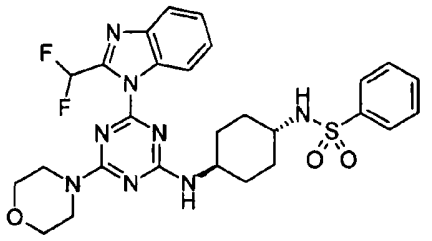
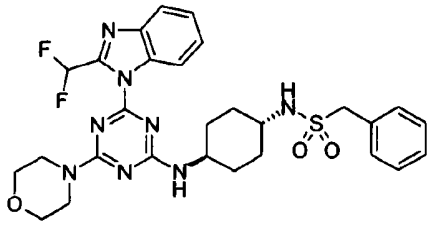
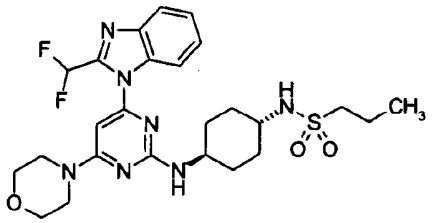
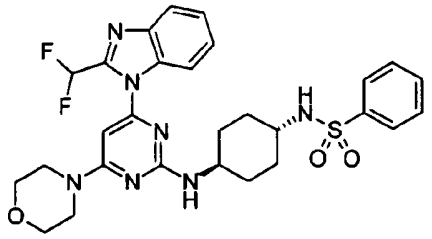
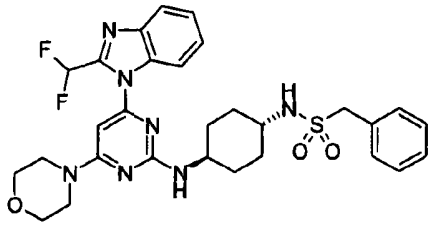
Ex	Str
73	
74	
75	
76	
77	

Ex	Str
78	
79	
80	
81	
82	

[0450] [表 26]

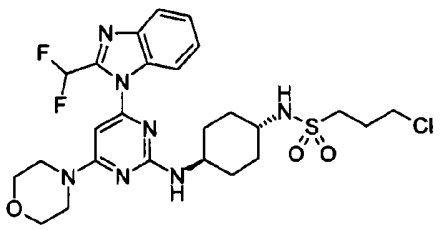
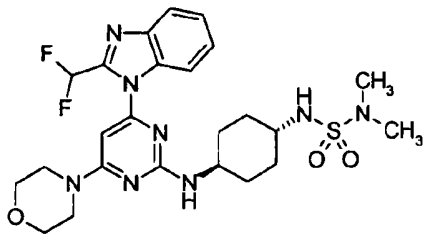
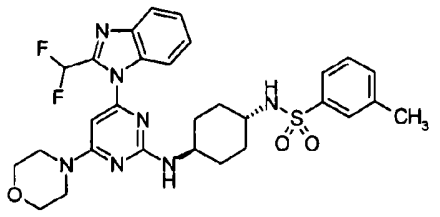
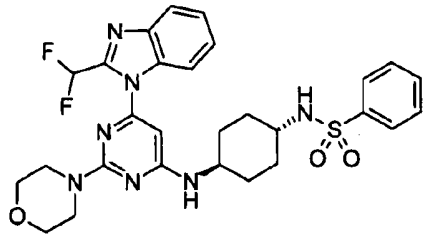
[0451]

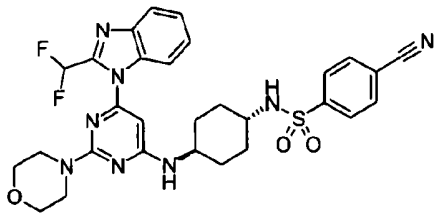
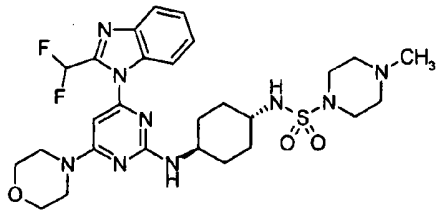
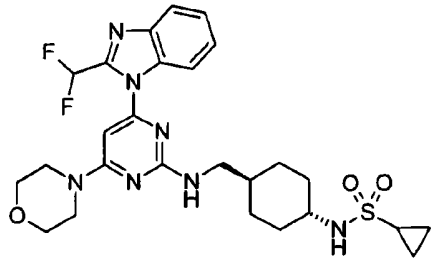
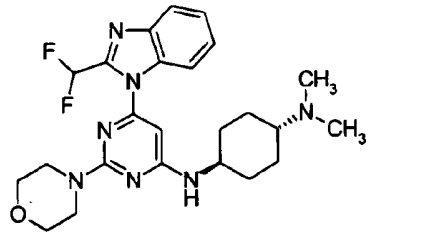
Ex	Str
83	
84	
85	
86	

Ex	Str
87	
88	
89	
90	
91	

[0452] [表 27]

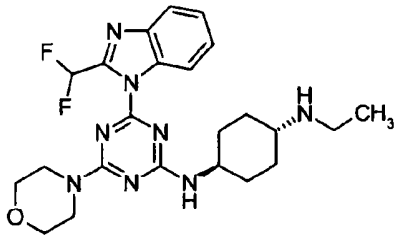
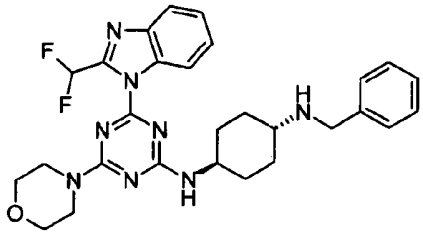
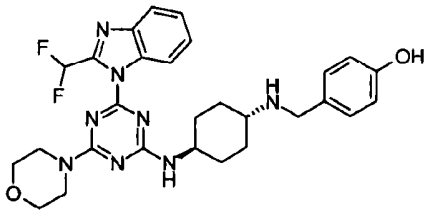
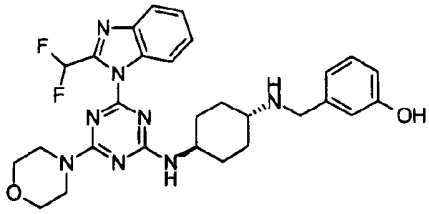
[0453]

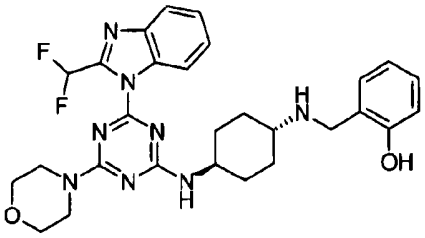
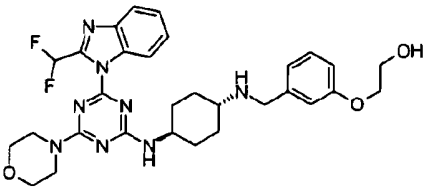
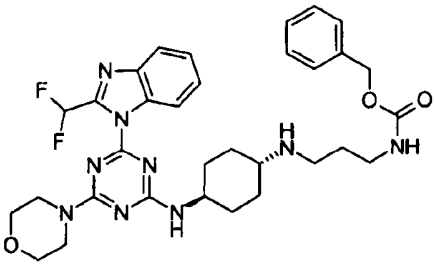
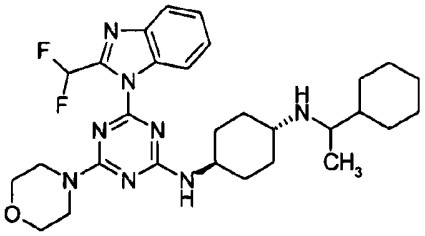
Ex	Str
92	
93	
94	
95	

Ex	Str
96	
97	
98	
99	

[0454] [表 28]

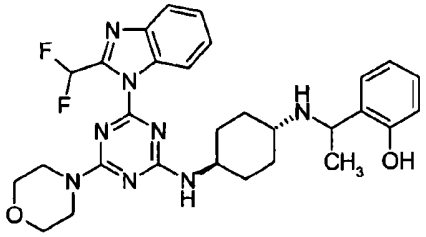
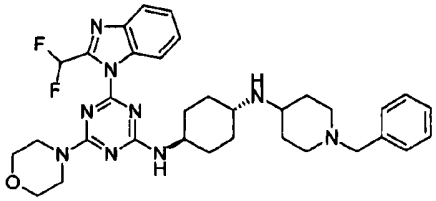
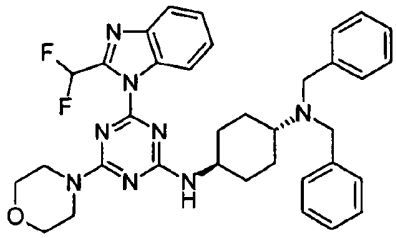
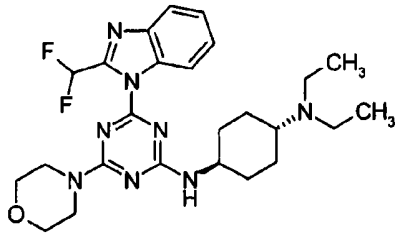
[0455]

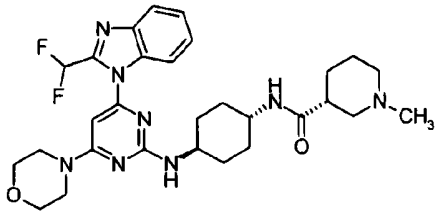
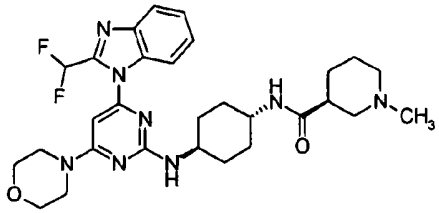
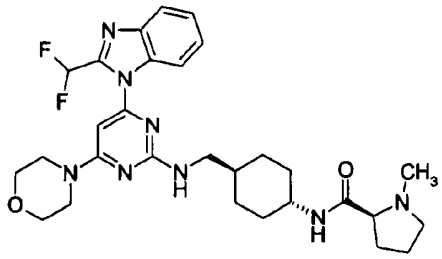
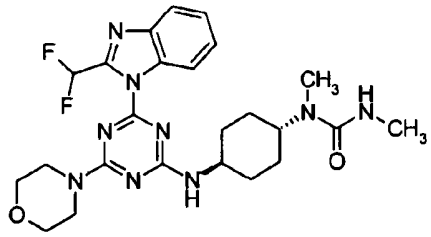
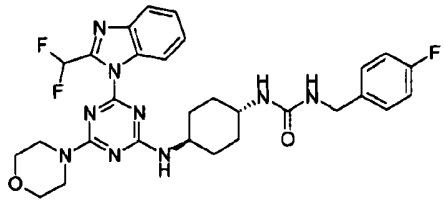
Ex	Str
100	
101	
102	
103	

Ex	Str
104	
105	
106	
107	

[0456] [表 29]

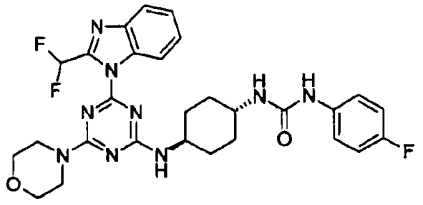
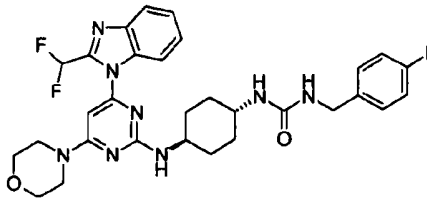
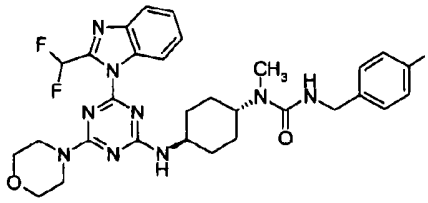
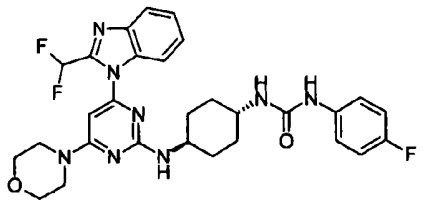
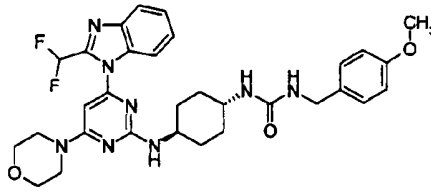
[0457]

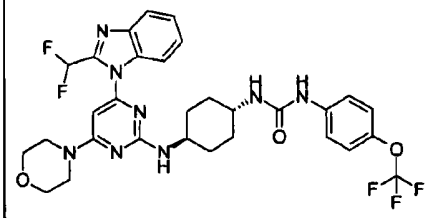
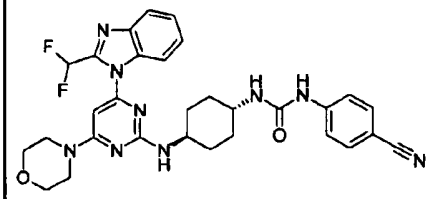
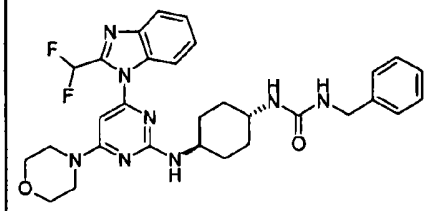
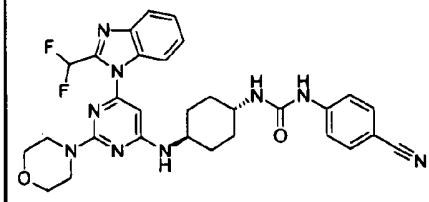
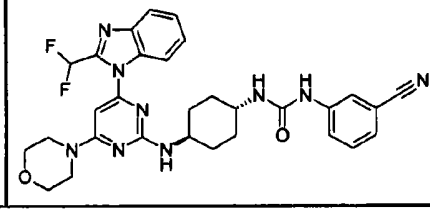
Ex	Str
108	
109	
110	
111	

Ex	Str
112	
113	
114	
115	
116	

[0458] [表 30]

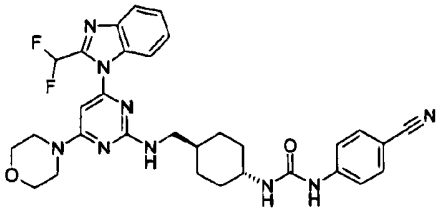
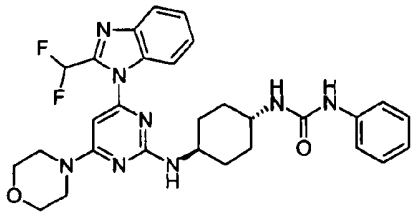
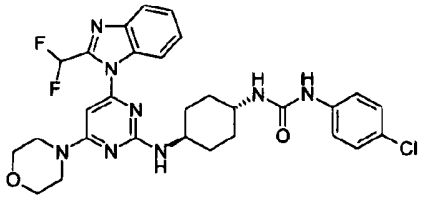
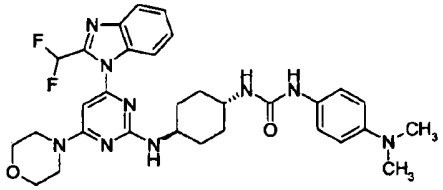
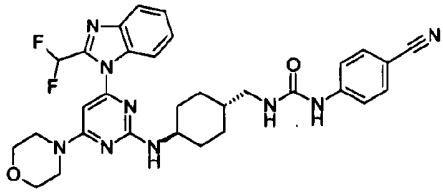
[0459]

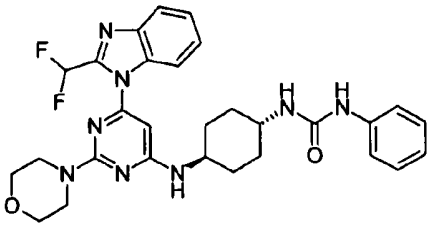
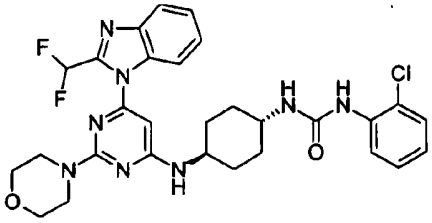
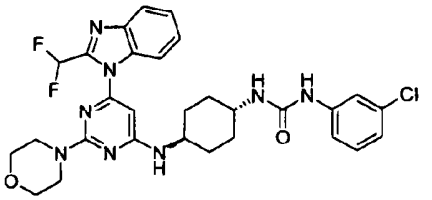
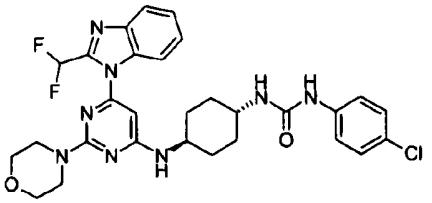
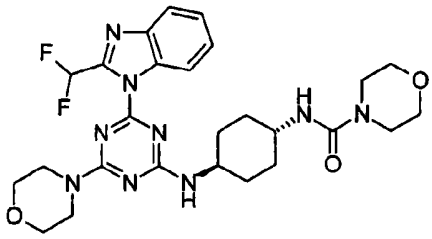
Ex	Str
117	
118	
119	
120	
121	

Ex	Str
122	
123	
124	
125	
126	

[0460] [表 31]

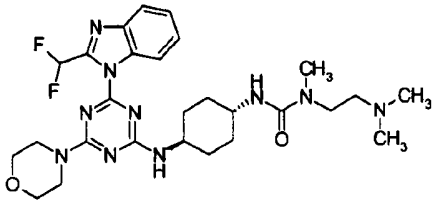
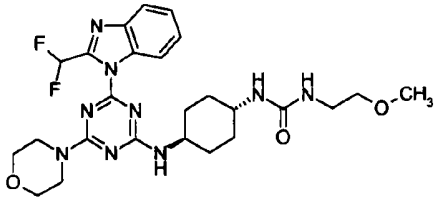
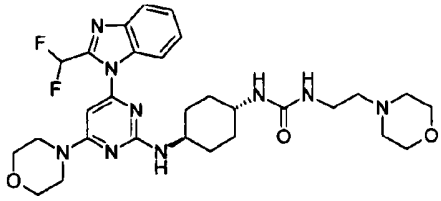
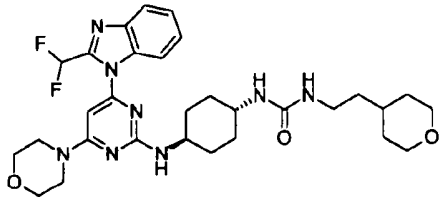
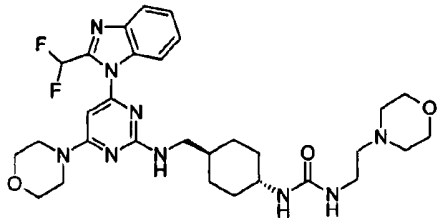
[0461]

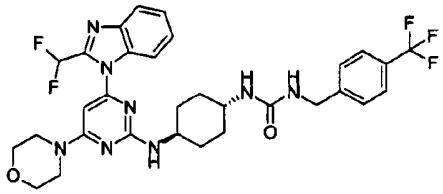
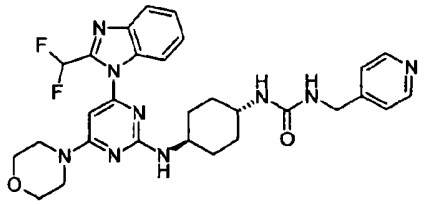
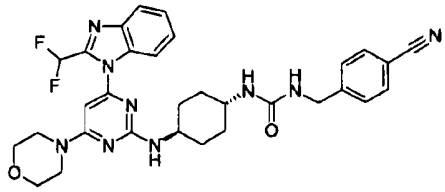
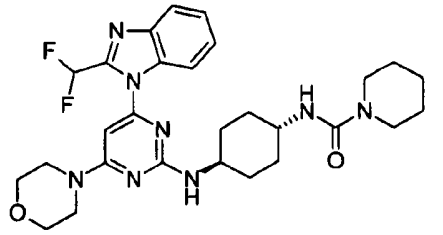
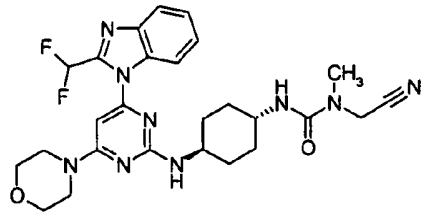
Ex	Str
127	
128	
129	
130	
131	

Ex	Str
132	
133	
134	
135	
136	

[0462] [表 32]

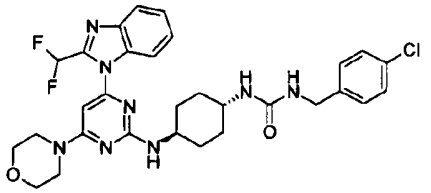
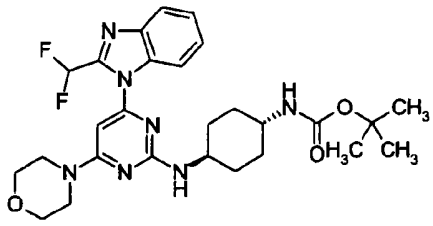
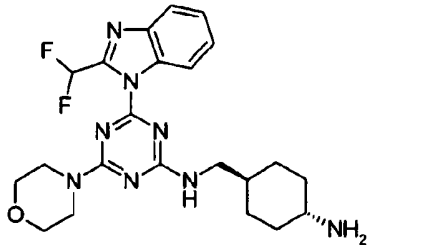
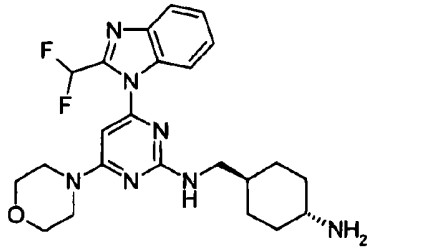
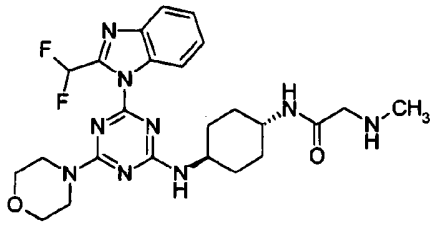
[0463]

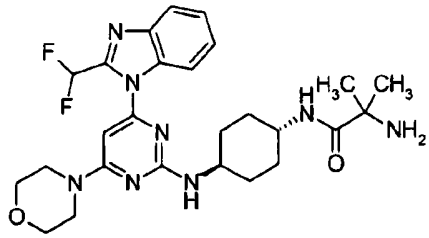
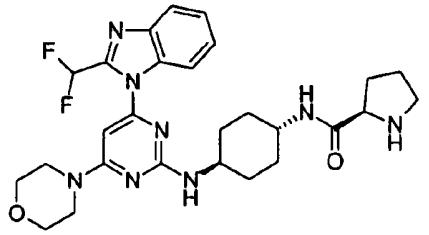
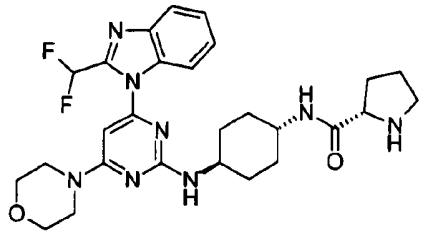
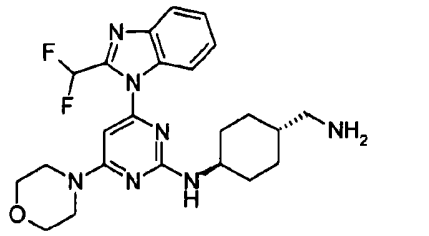
Ex	Str
137	
138	
139	
140	
141	

Ex	Str
142	
143	
144	
145	
146	

[0464] [表 33]

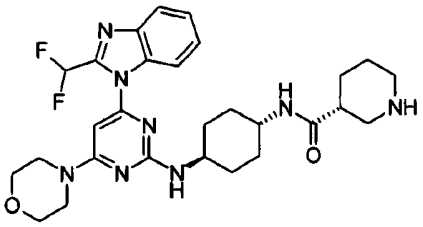
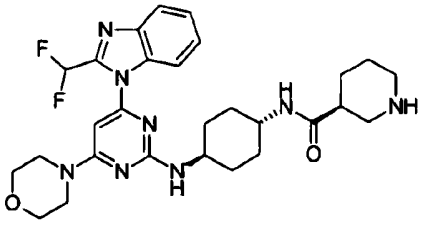
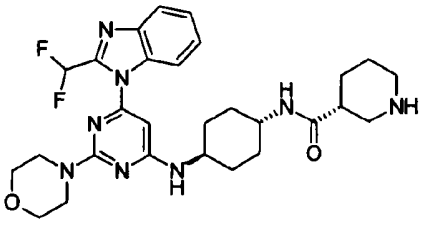
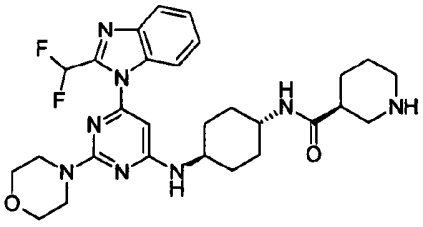
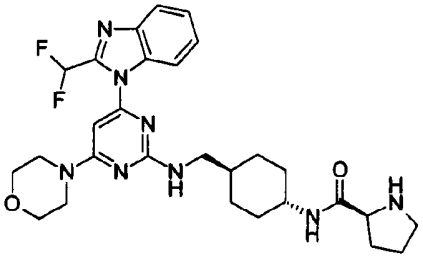
[0465]

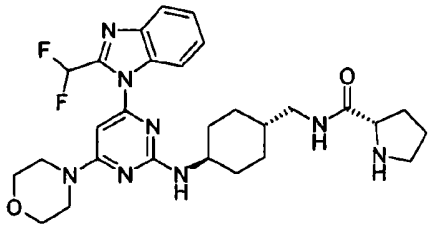
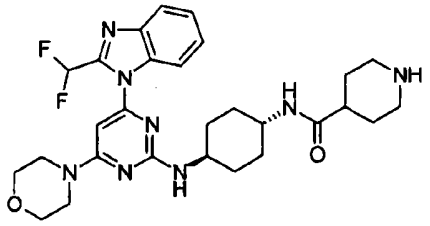
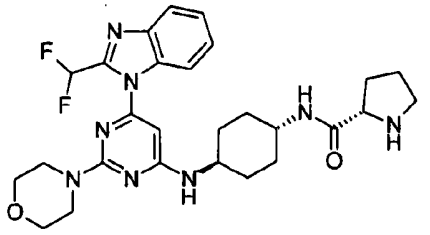
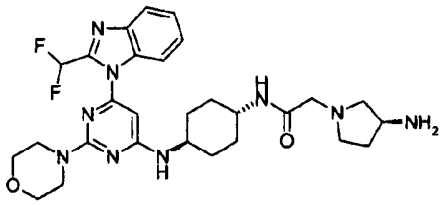
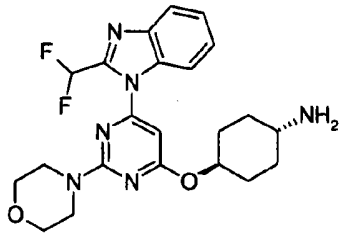
Ex	Str
147	
148	
149	
150	
151	

Ex	Str
152	
153	
154	
155	

[0466] [表 34]

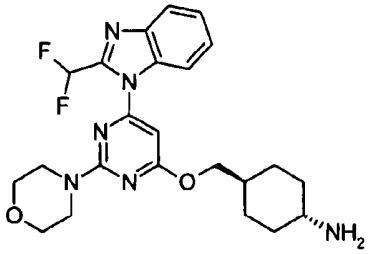
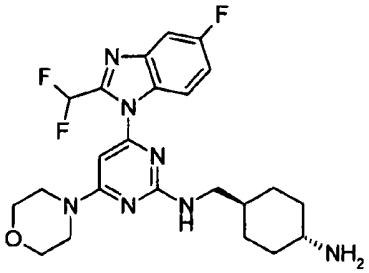
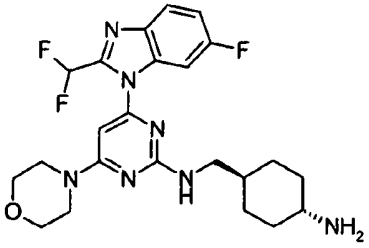
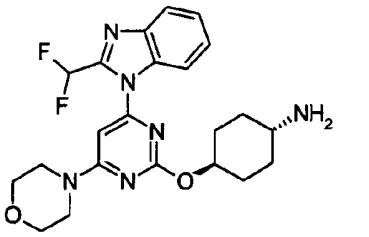
[0467]

Ex	Str
156	
157	
158	
159	
160	

Ex	Str
161	
162	
163	
164	
165	

[0468] [表 35]

[0469]

Ex	Str
166	
167	
168	
169	

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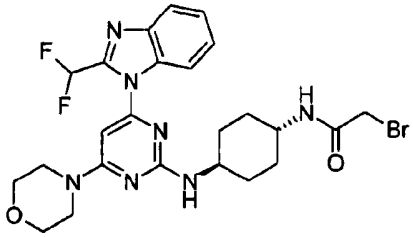
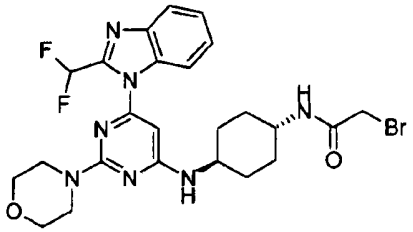
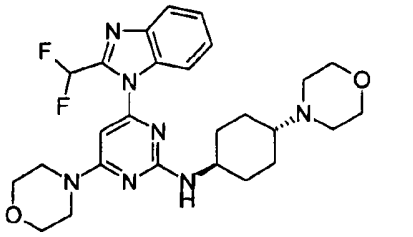
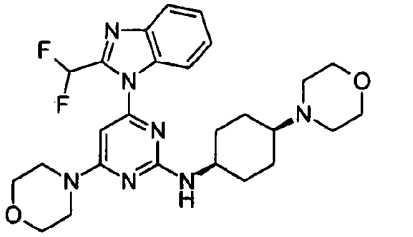
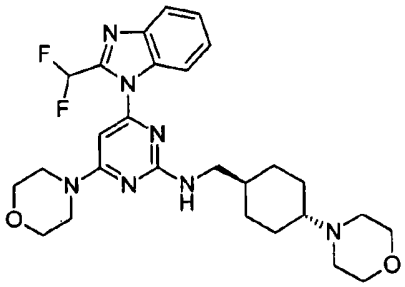
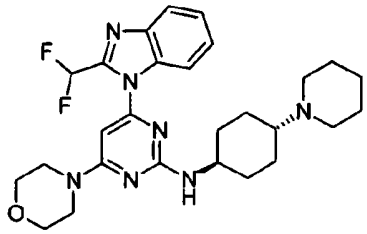
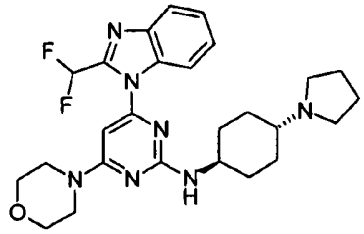
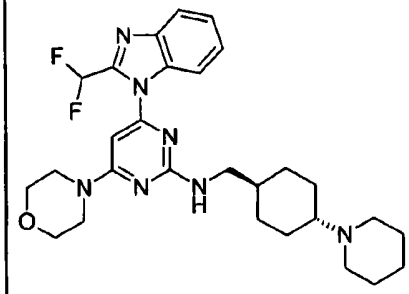
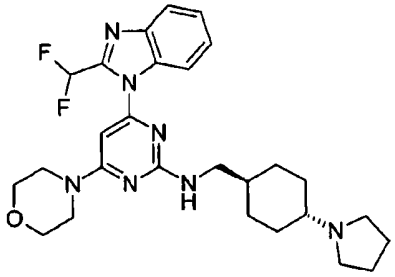
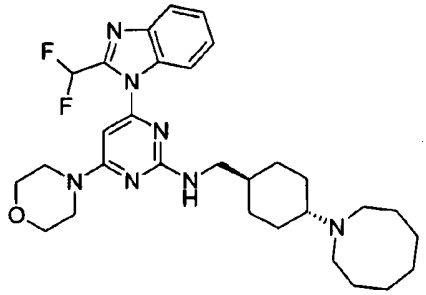
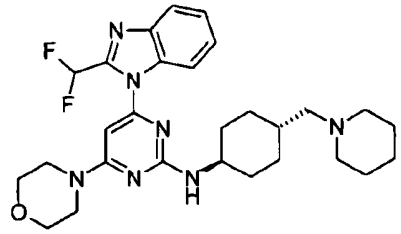
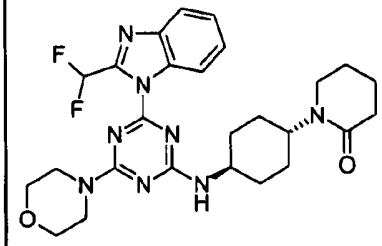
170	
171	
172	
173	

[0470] [表 36]

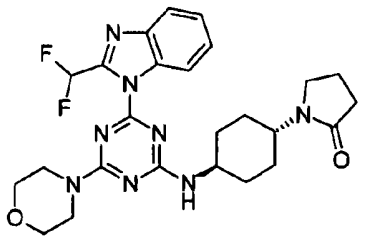
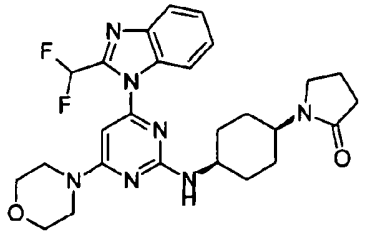
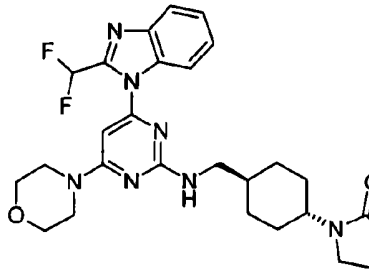
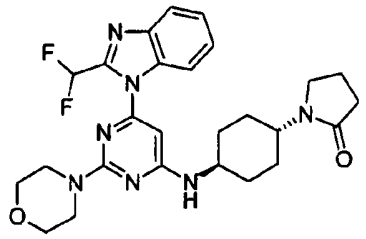
[0471]

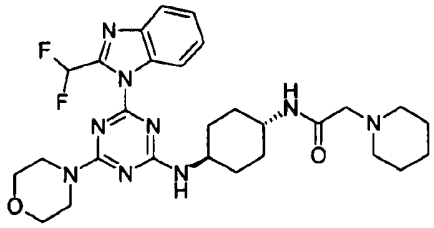
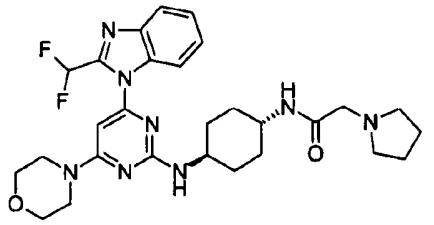
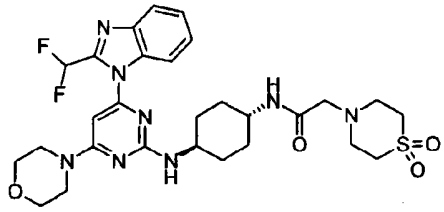
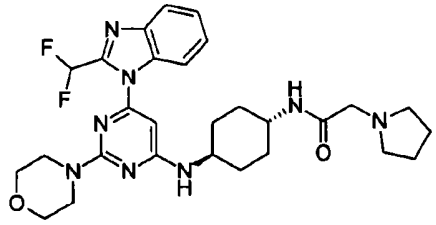
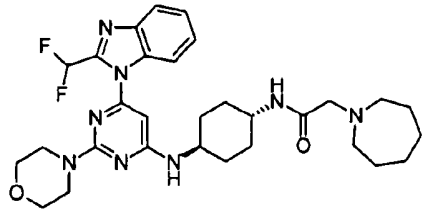
Ex	Str
174	
175	
176	
177	

Ex	Str
178	
179	
180	
181	

[0472] [表 37]

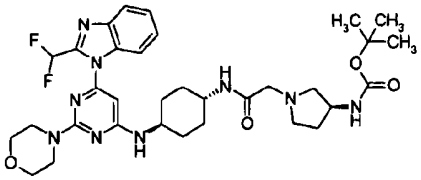
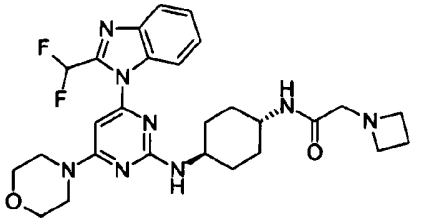
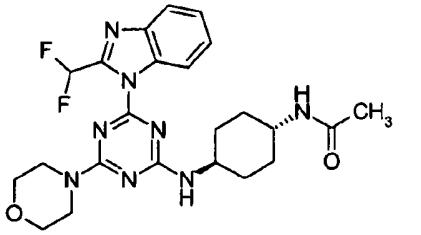
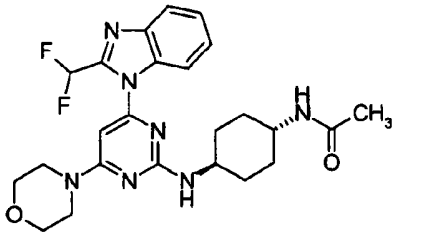
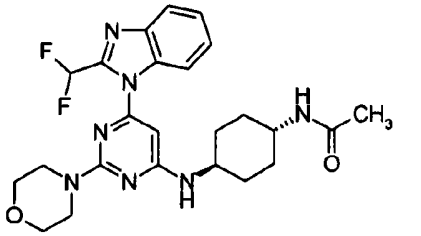
[0473]

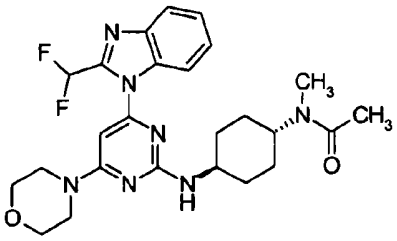
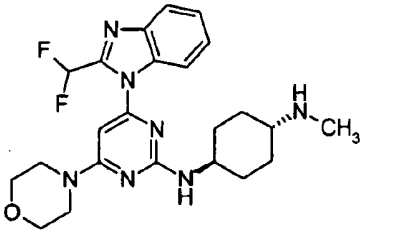
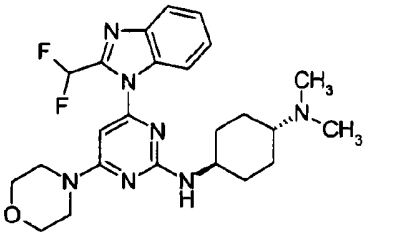
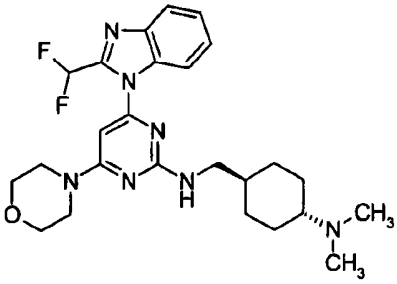
Ex	Str
182	
183	
184	
185	

Ex	Str
186	
187	
188	
189	
190	

[0474] [表 38]

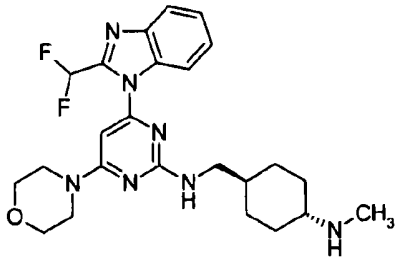
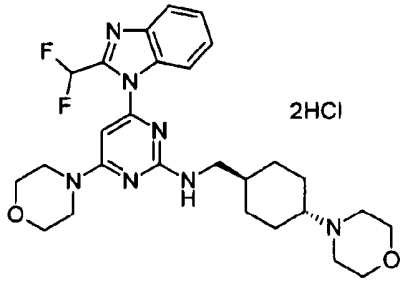
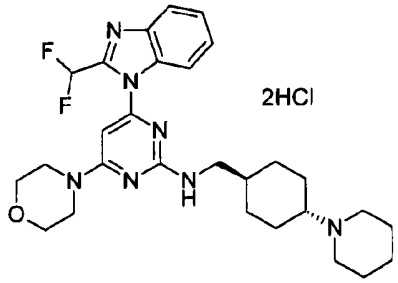
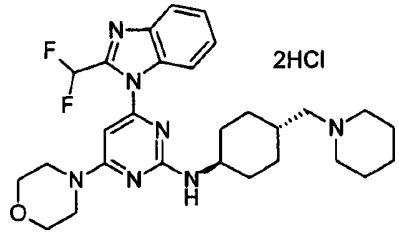
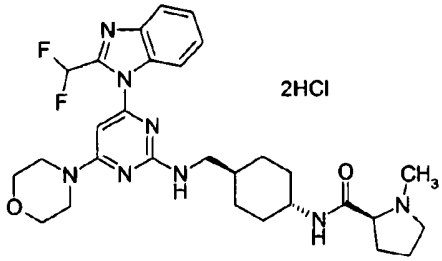
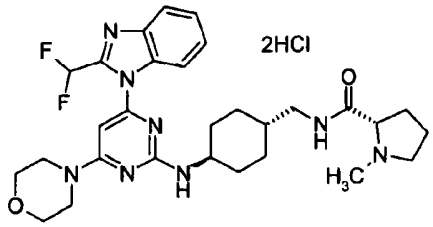
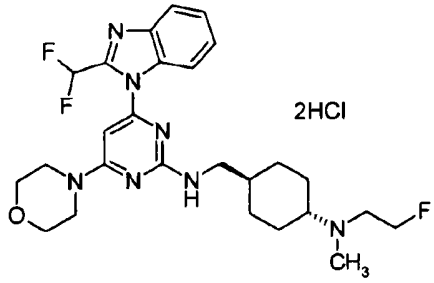
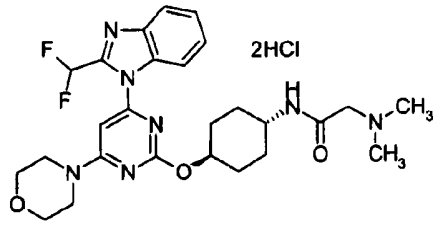
[0475]

Ex	Str
191	
192	
193	
194	
195	

Ex	Str
196	
197	
198	
199	

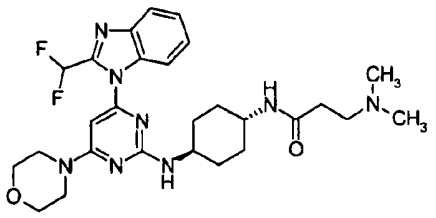
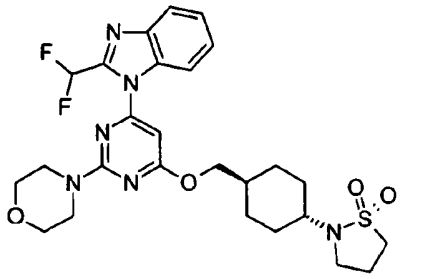
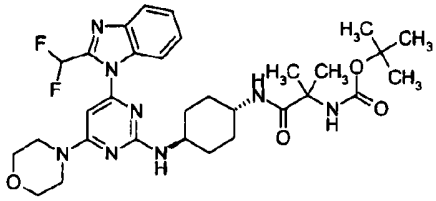
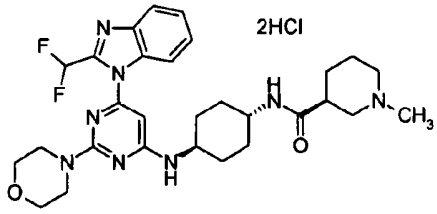
[0476] [表 39]

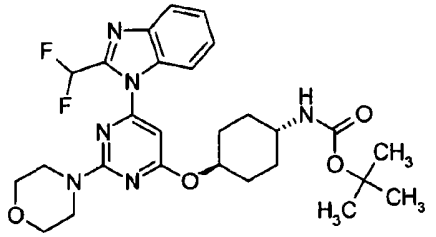
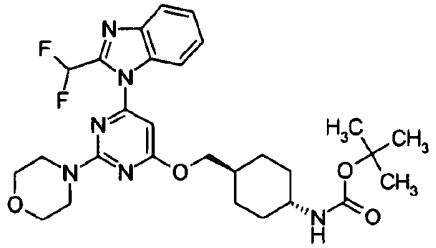
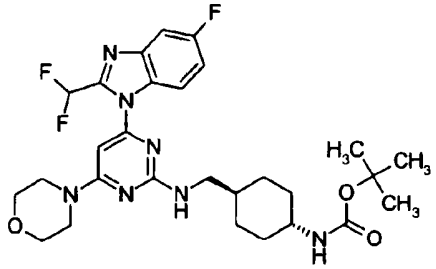
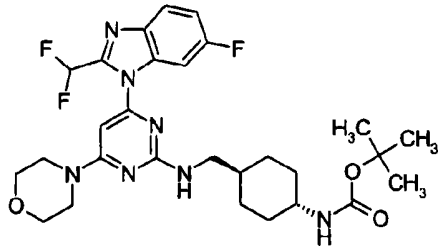
[0477]

Ex	Str
200	
201	
202	
203	
204	
205	
206	
207	

[0478] [表 40]

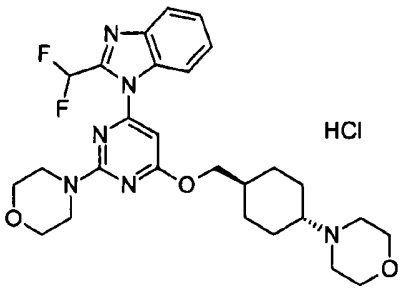
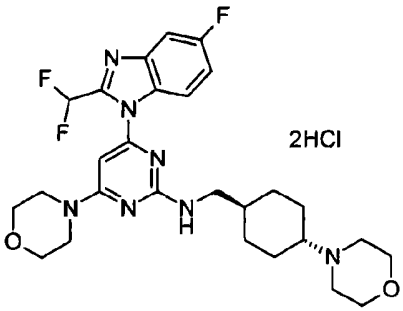
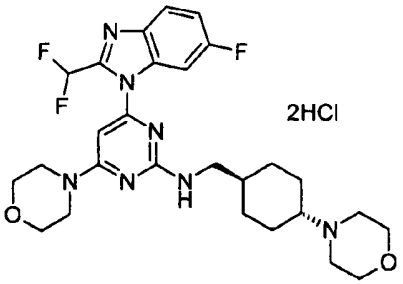
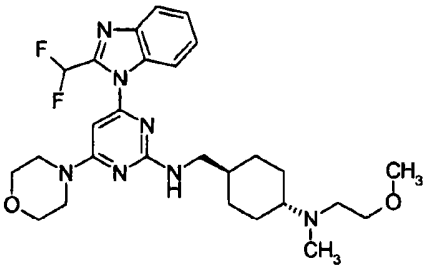
[0479]

Ex	Str
208	
209	
210	
211	

Ex	Str
212	
213	
214	
215	

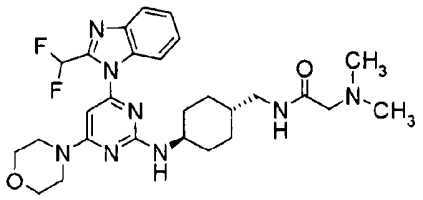
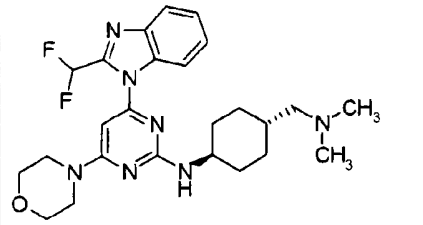
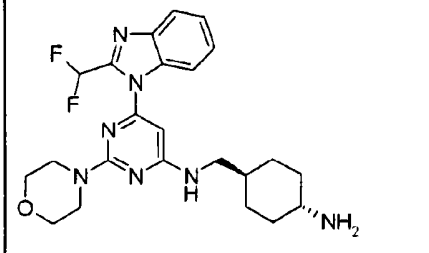
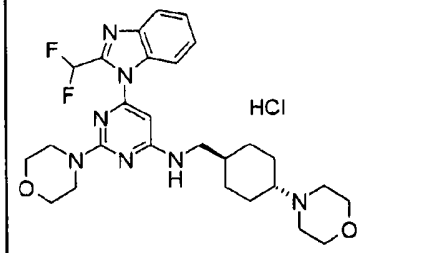
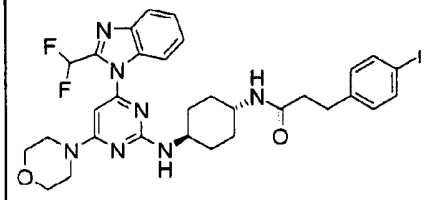
[0480] [表 41]

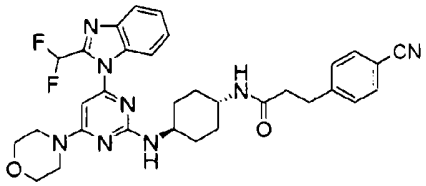
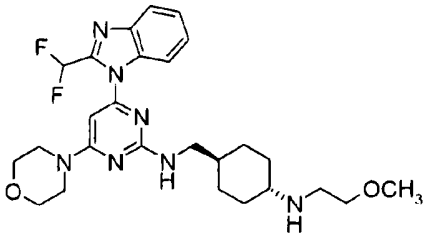
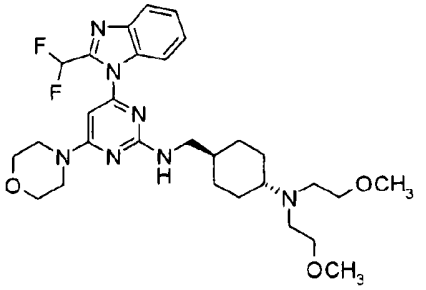
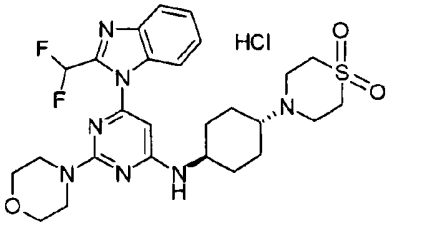
[0481]

Ex	Str
216	 HCl
217	 2HCl
218	 2HCl
219	

[0482] [表 42]

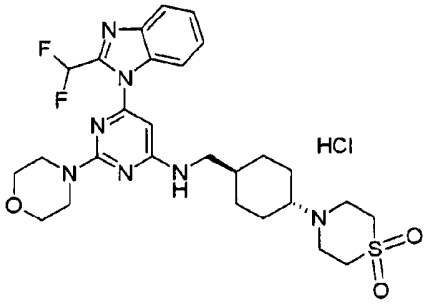
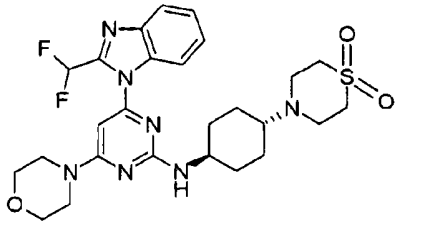
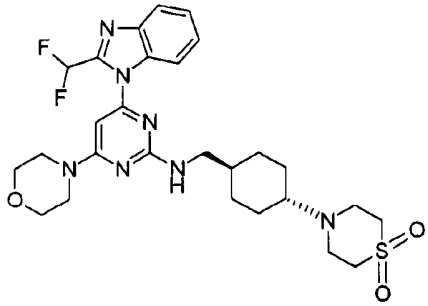
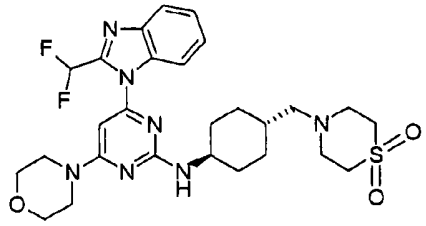
[0483]

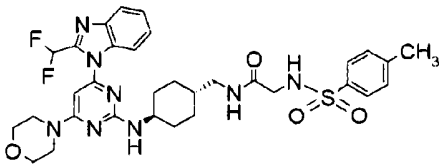
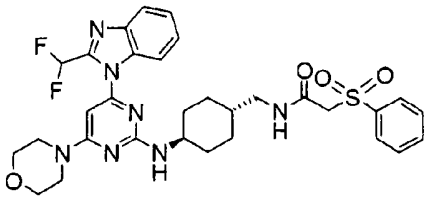
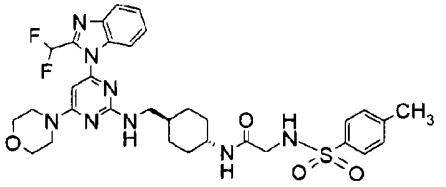
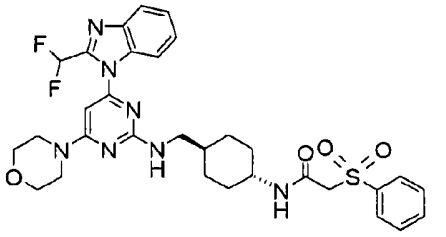
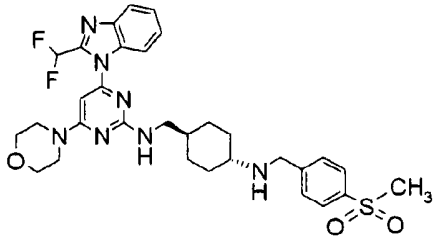
Ex	Str
220	
221	
222	
223	
224	

Ex	Str
225	
226	
227	
228	

[0484] [表 43]

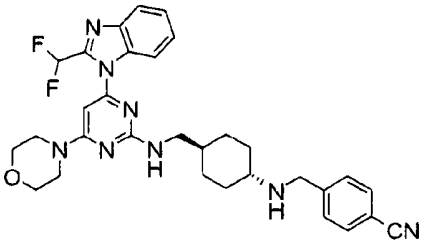
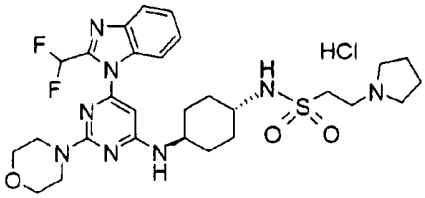
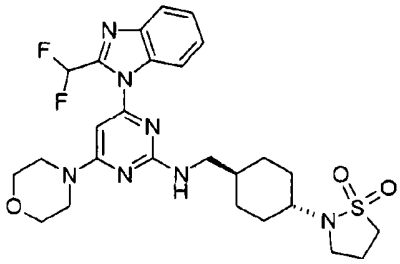
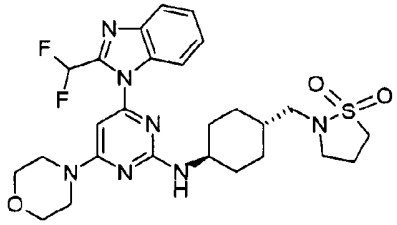
[0485]

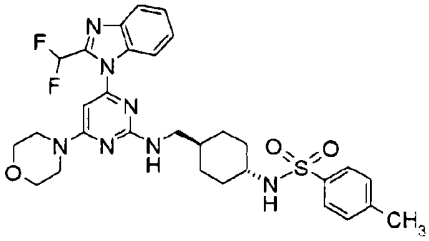
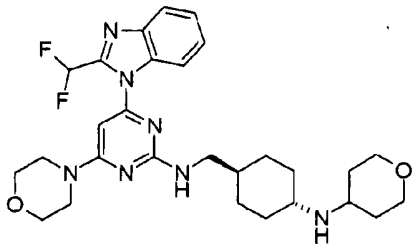
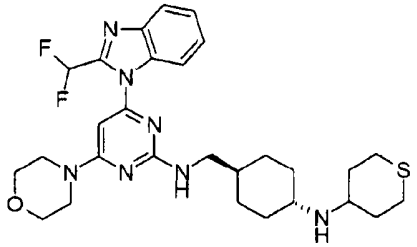
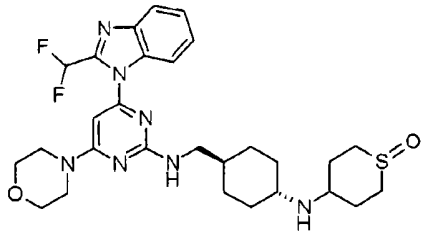
Ex	Str
229	
230	
231	
232	

Ex	Str
233	
234	
235	
236	
237	

[0486] [表 44]

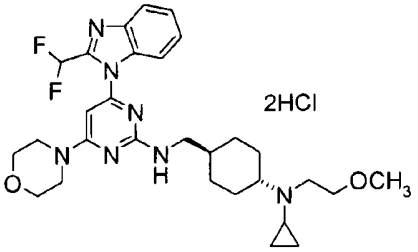
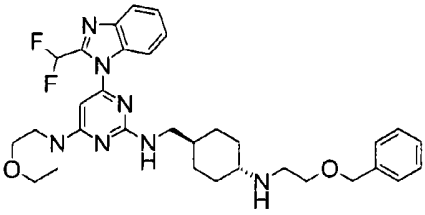
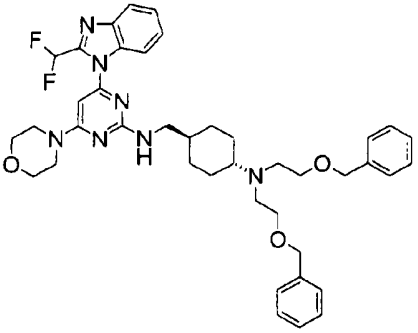
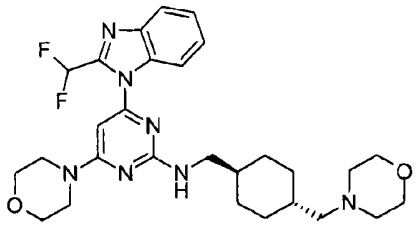
[0487]

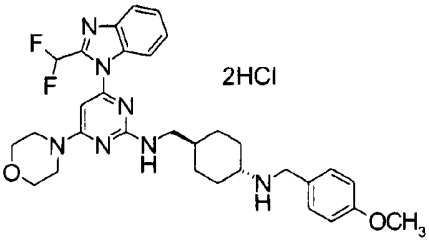
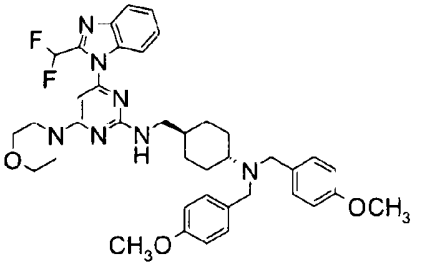
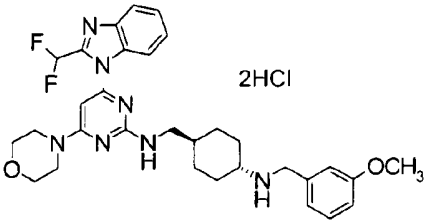
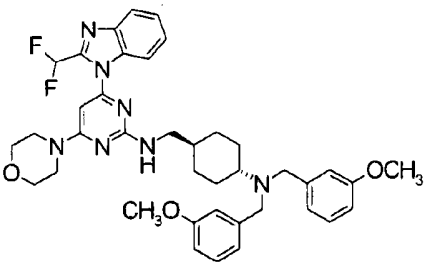
Ex	Str
238	
239	
240	
241	

Ex	Str
242	
243	
244	
245	

[0488] [表 45]

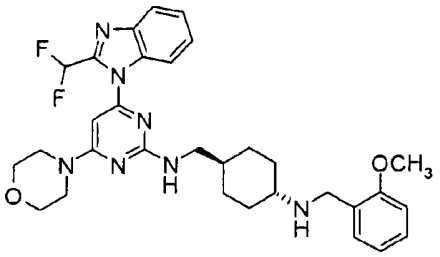
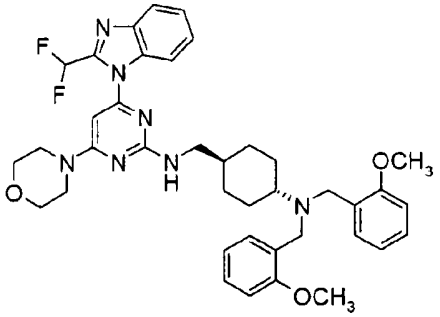
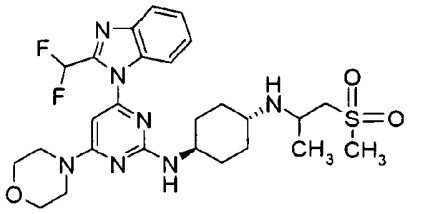
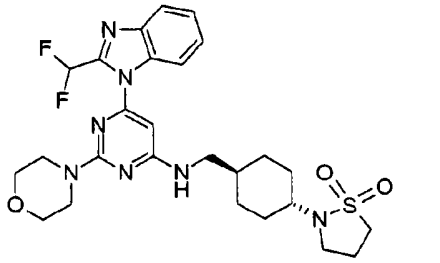
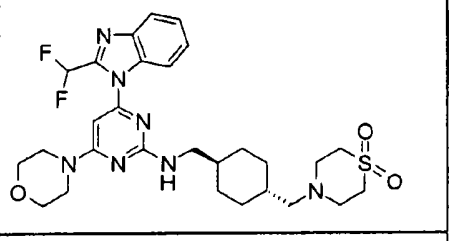
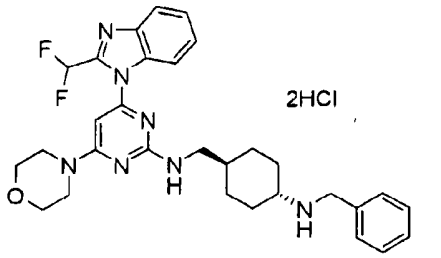
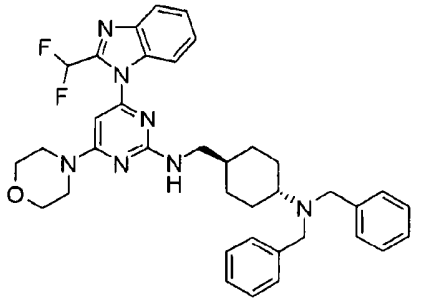
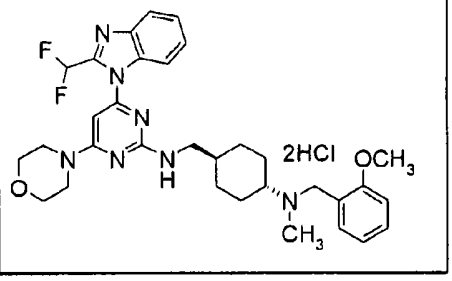
[0489]

Ex	Str
246	
247	
248	
249	

Ex	Str
250	
251	
252	
253	

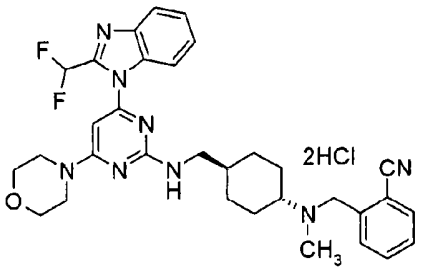
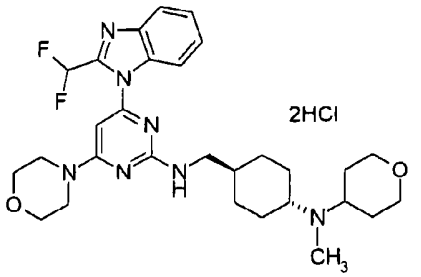
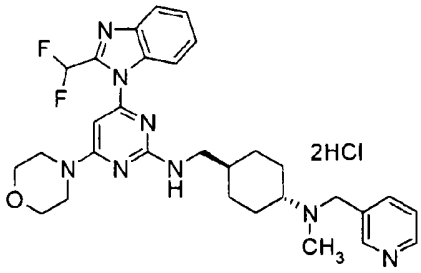
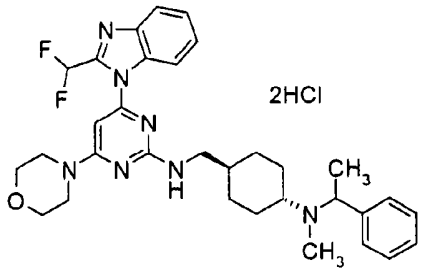
[0490] [表 46]

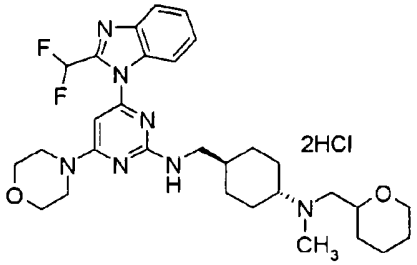
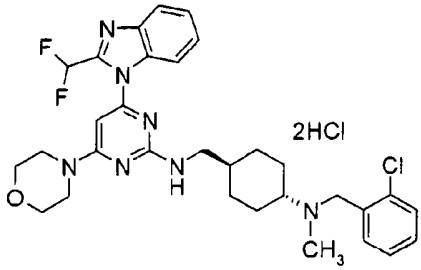
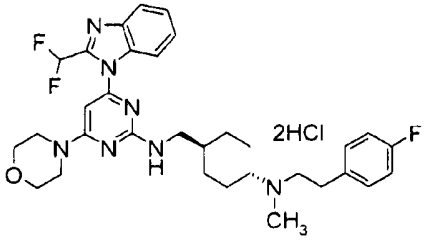
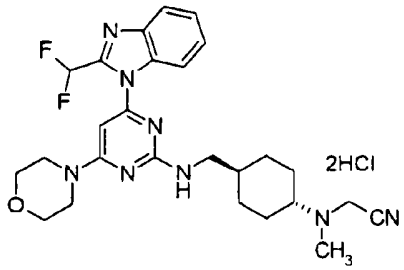
[0491]

Ex	Str
254	
255	
256	
257	
258	
259	
260	
261	

[0492] [表 47]

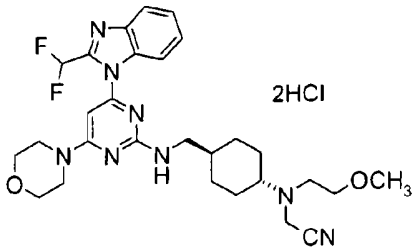
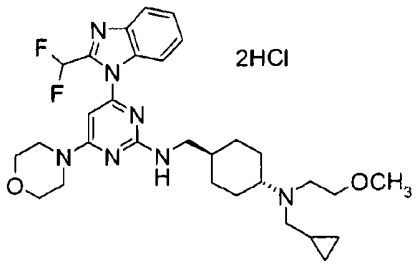
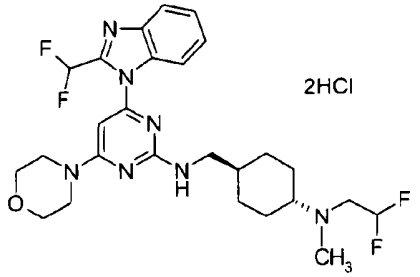
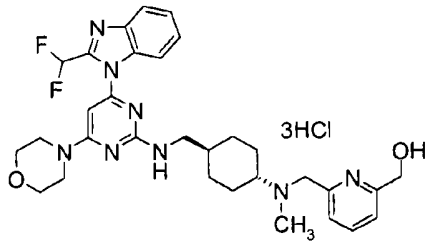
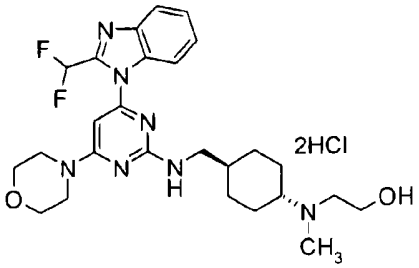
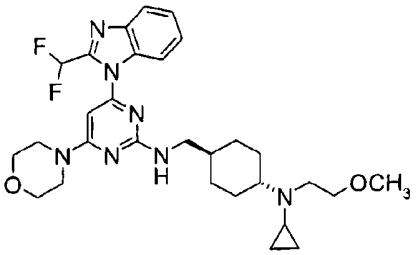
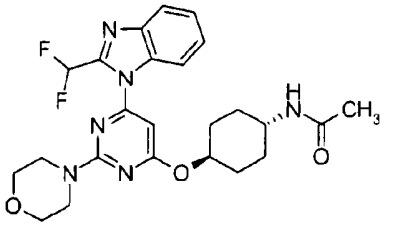
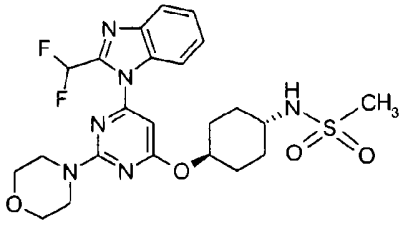
[0493]

Ex	Str
262	
263	
264	
265	

Ex	Str
266	
267	
268	
269	

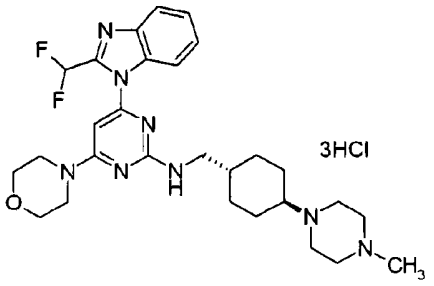
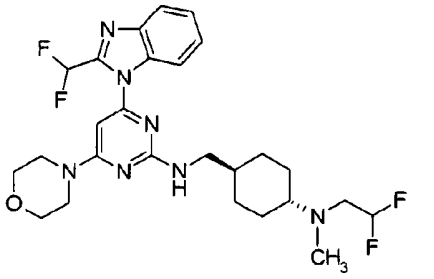
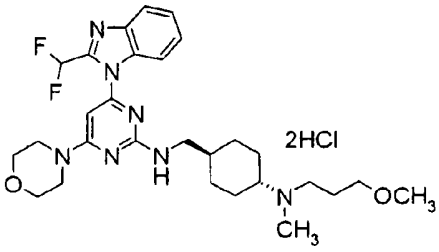
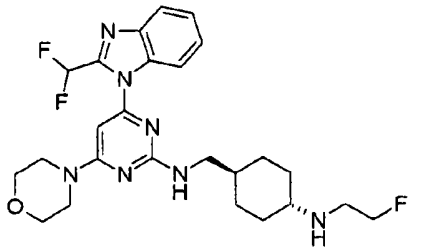
[0494] [表 48]

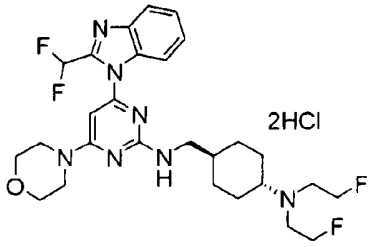
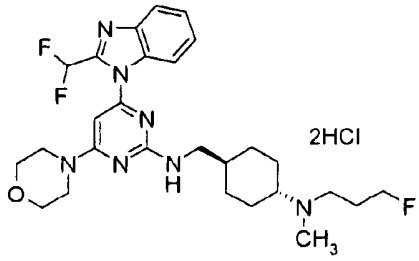
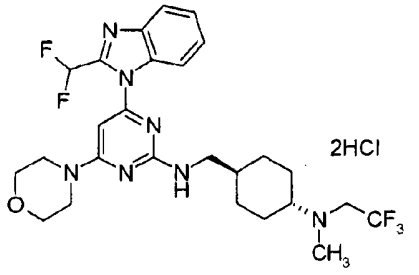
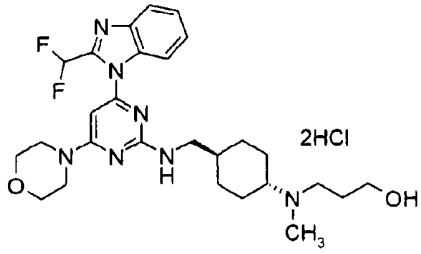
[0495]

Ex	Str
270	
271	
272	
273	
274	
275	
276	
277	

[0496] [表 49]

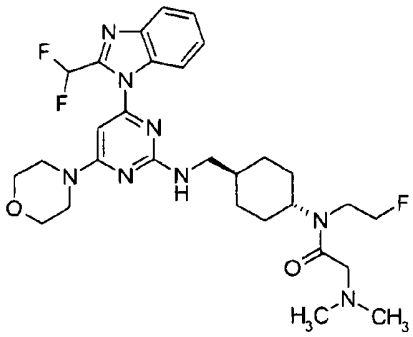
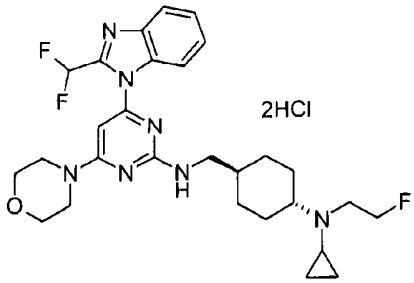
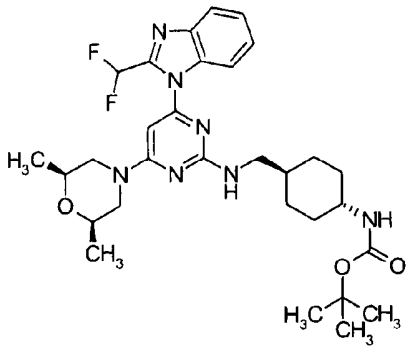
[0497]

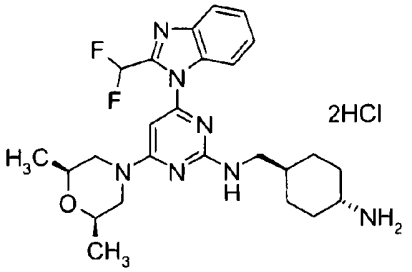
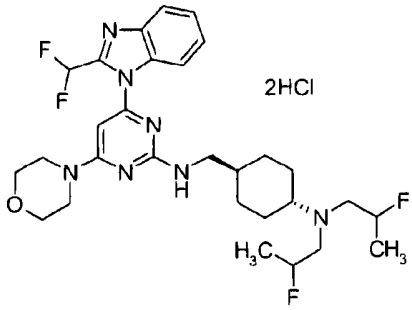
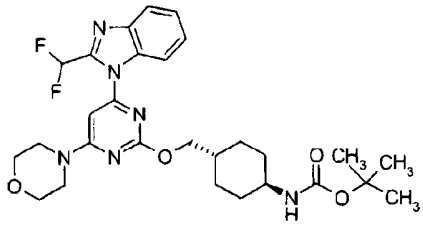
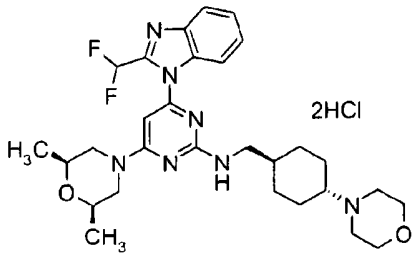
Ex	Str
278	
279	
280	
281	

Ex	Str
282	
283	
284	
285	

[0498] [表 50]

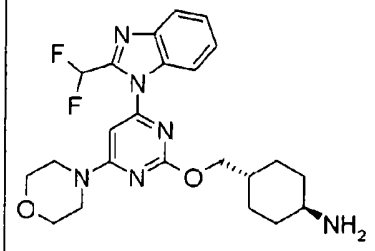
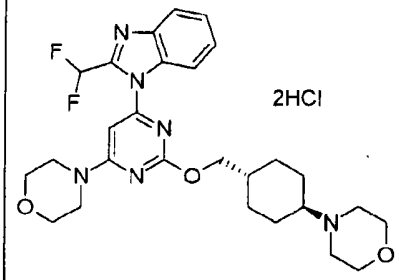
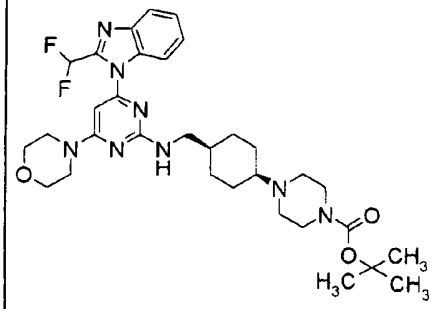
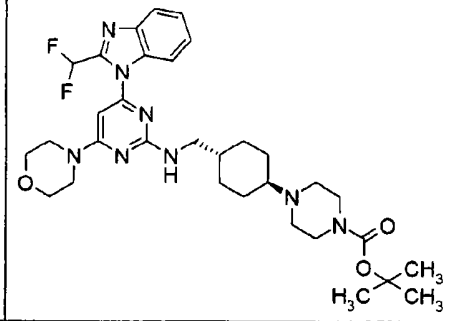
[0499]

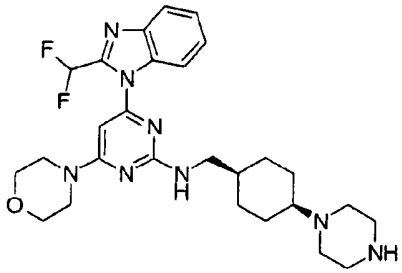
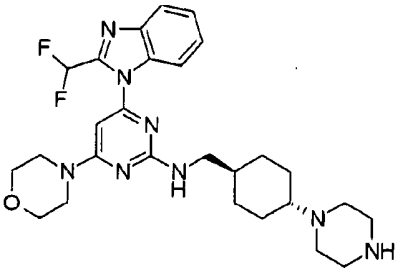
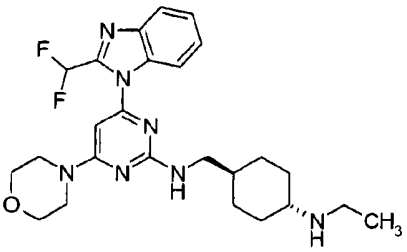
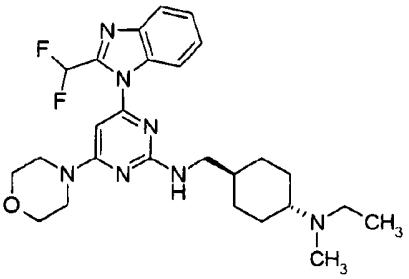
Ex	Str
286	
287	
288	

Ex	Str
289	
290	
291	
292	

[0500] [表 51]

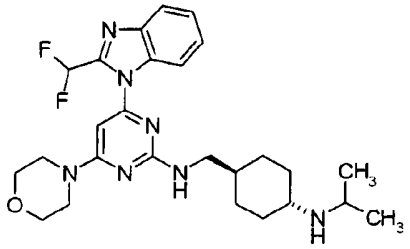
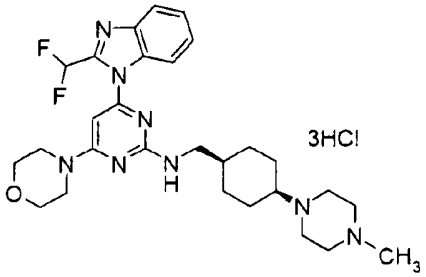
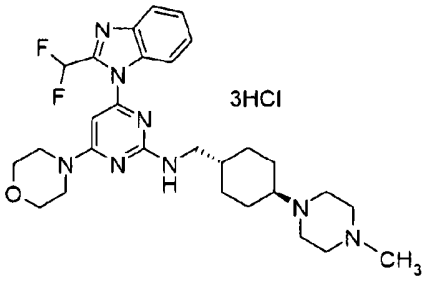
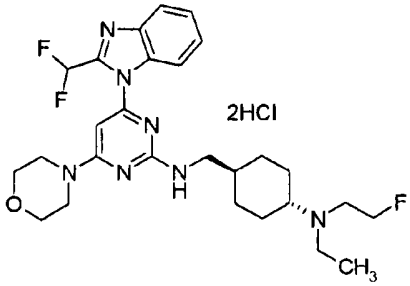
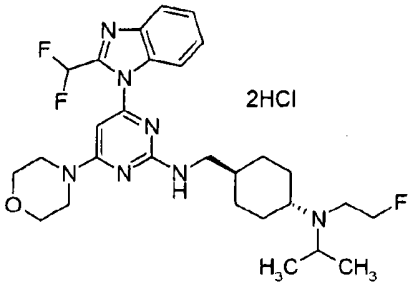
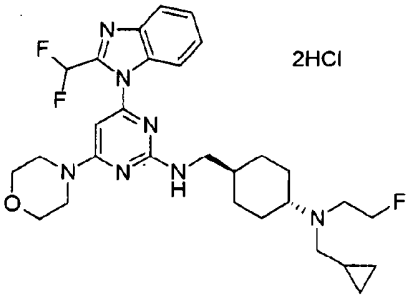
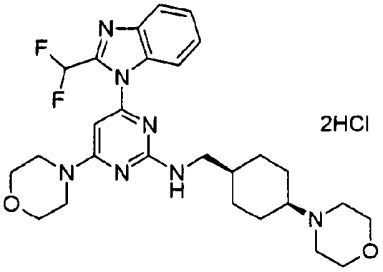
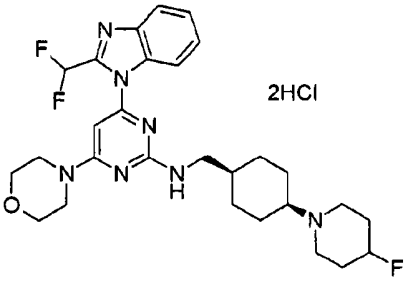
[0501]

Ex	Str
293	
294	
295	
296	

Ex	Str
297	
298	
299	
300	

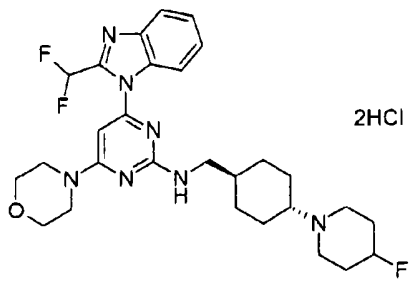
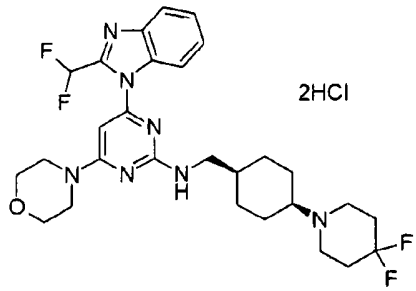
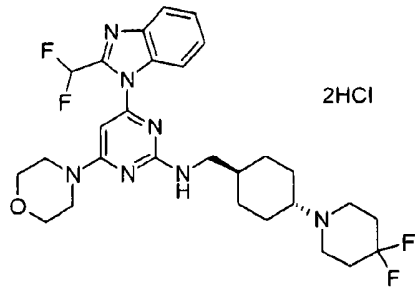
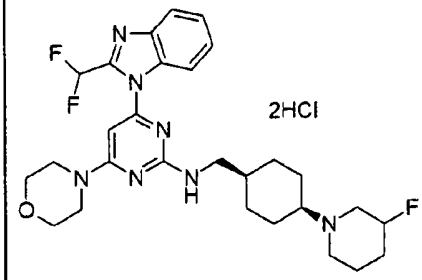
[0502] [表 52]

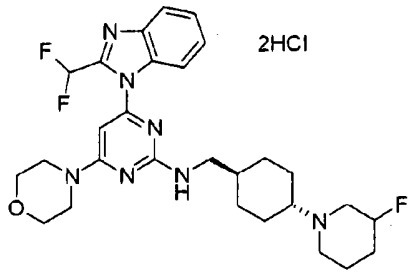
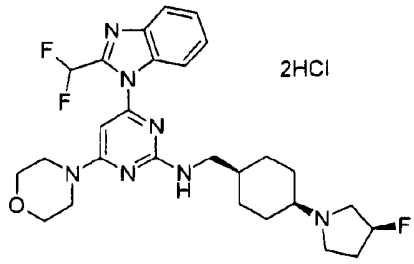
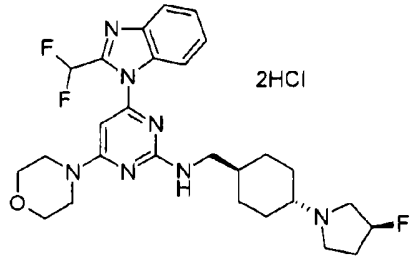
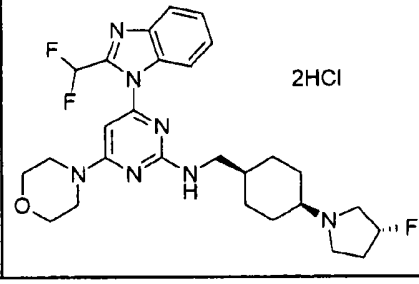
[0503]

Ex	Str
301	
302	 3HCl
303	 3HCl
304	 2HCl
305	 2HCl
306	 2HCl
307	 2HCl
308	 2HCl

[0504] [表 53]

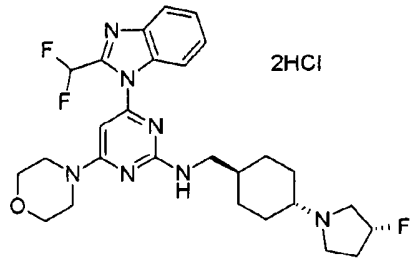
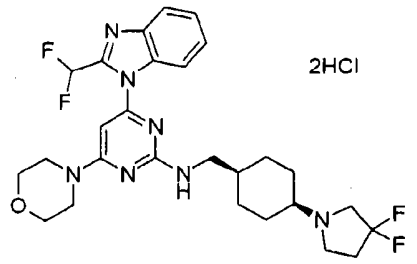
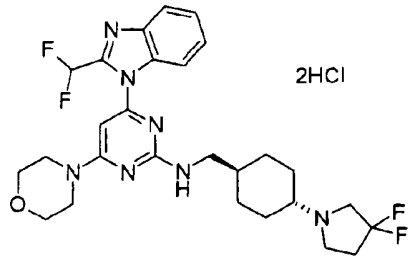
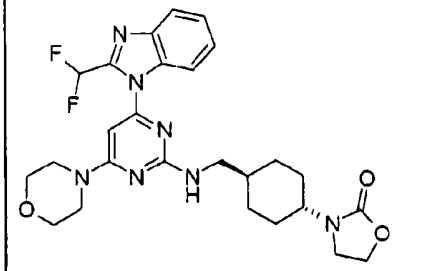
[0505]

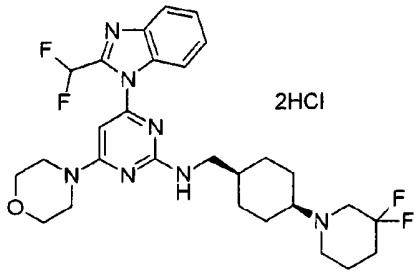
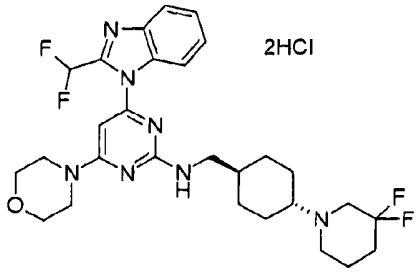
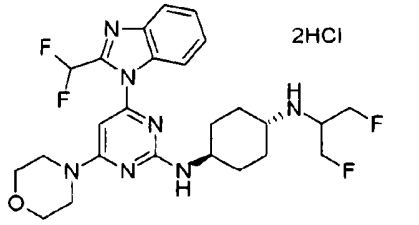
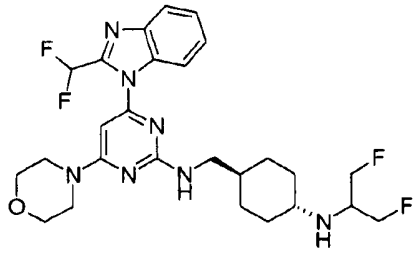
Ex	Str
309	
310	
311	
312	

Ex	Str
313	
314	
315	
316	

[0506] [表 54]

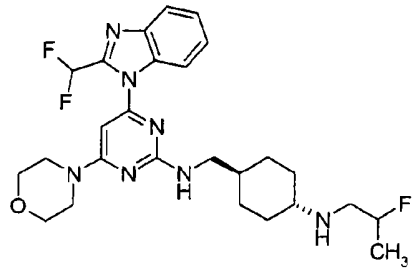
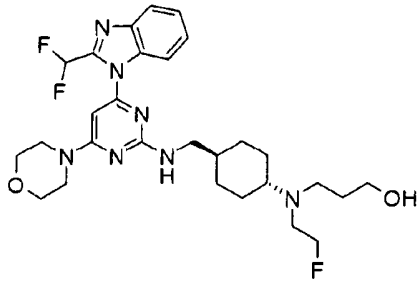
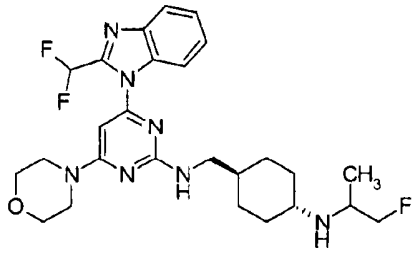
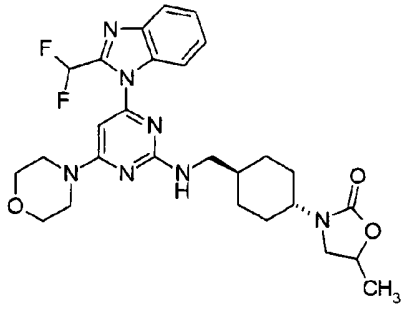
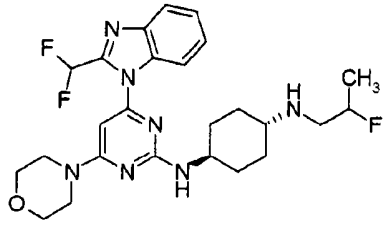
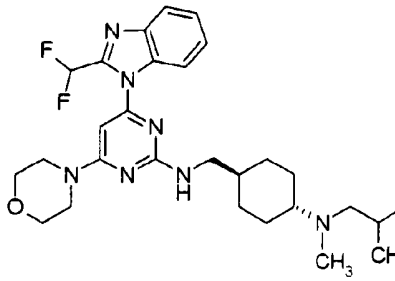
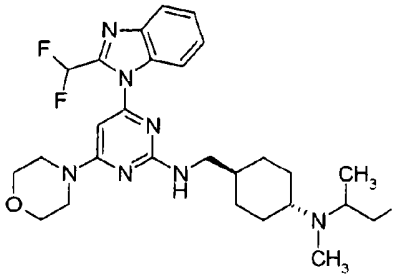
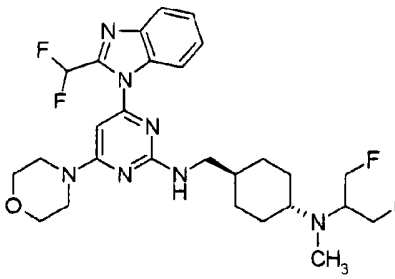
[0507]

Ex	Str
317	
318	
319	
320	

Ex	Str
321	
322	
323	
324	

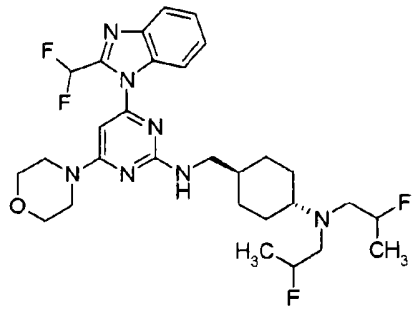
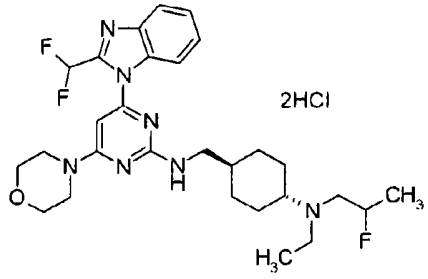
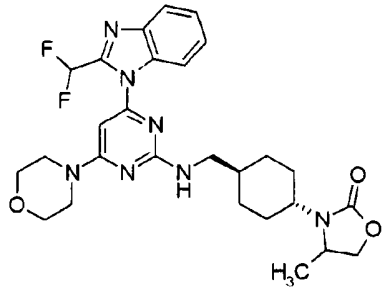
[0508] [表 55]

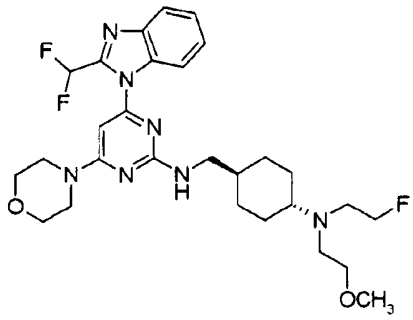
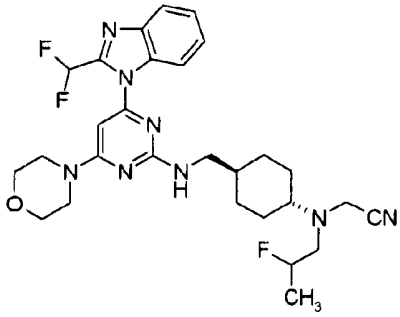
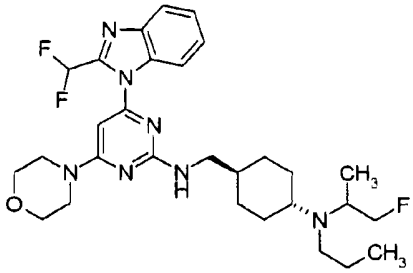
[0509]

Ex	Str
325	
326	
327	
328	
329	
330	
331	
332	

[0510] [表 56]

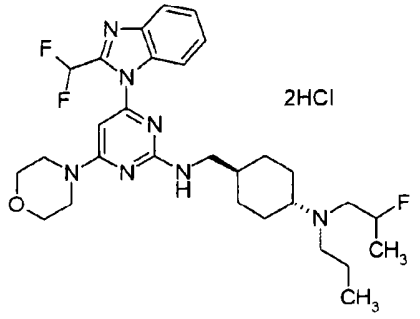
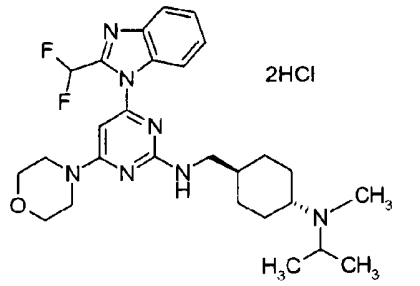
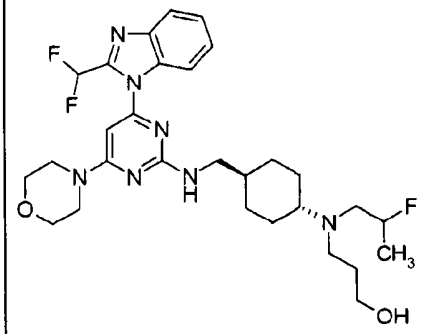
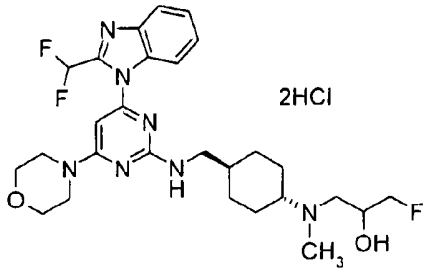
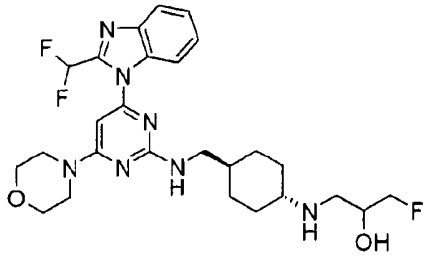
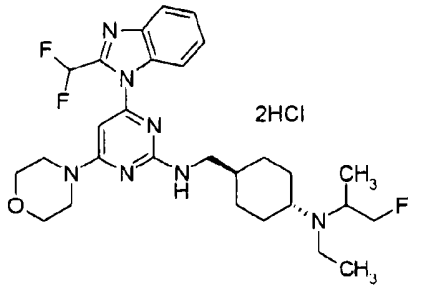
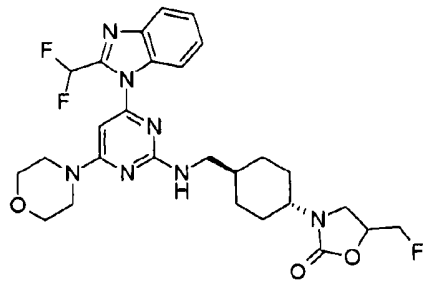
[0511]

Ex	Str
333	
334	
335	

Ex	Str
336	
337	
338	

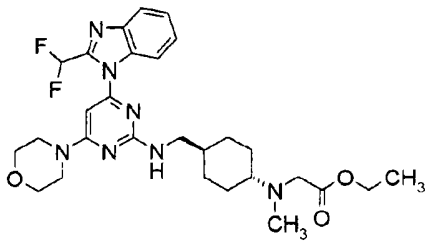
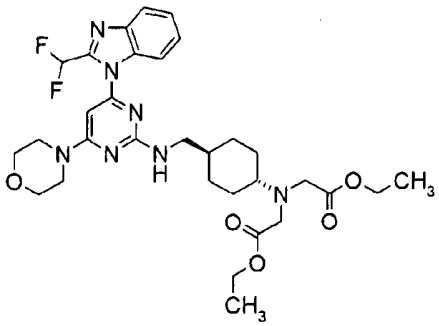
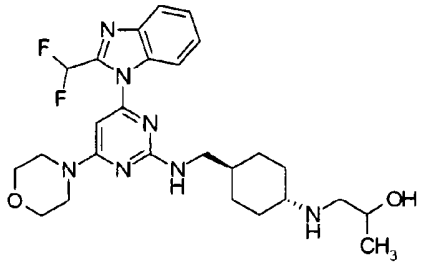
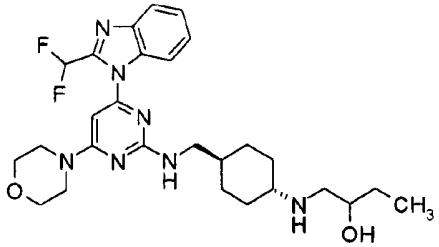
[0512] [表 57]

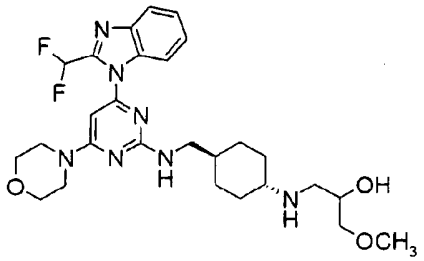
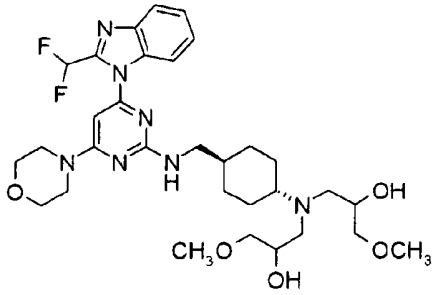
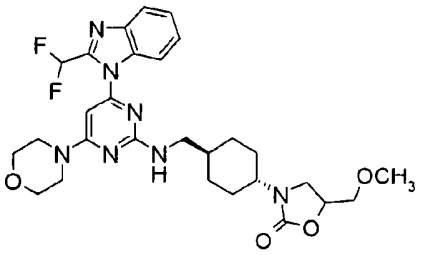
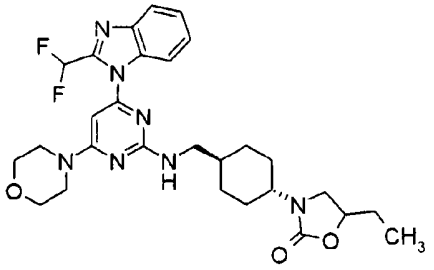
[0513]

Ex	Str
339	
340	
341	
342	
343	
344	
345	

[0514] [表 58]

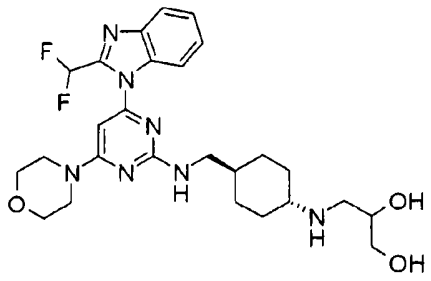
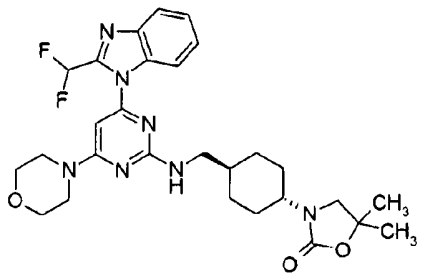
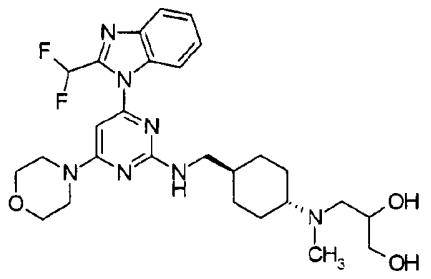
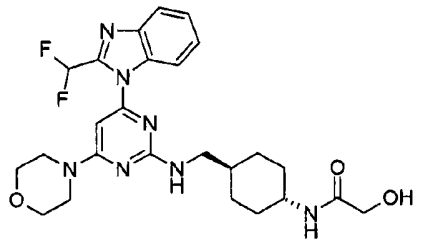
[0515]

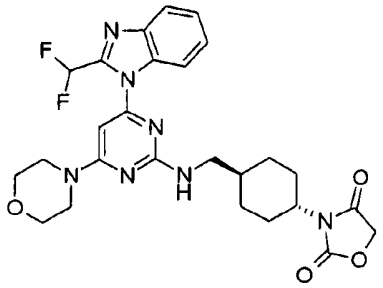
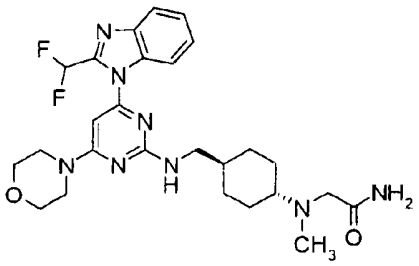
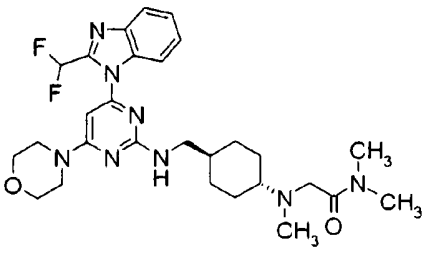
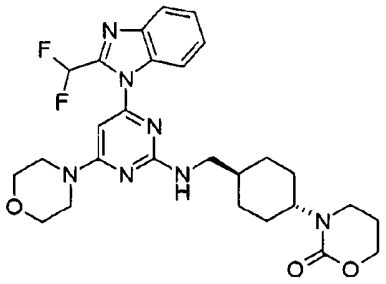
Ex	Str
346	
347	
348	
349	

Ex	Str
350	
351	
352	
353	

[0516] [表 59]

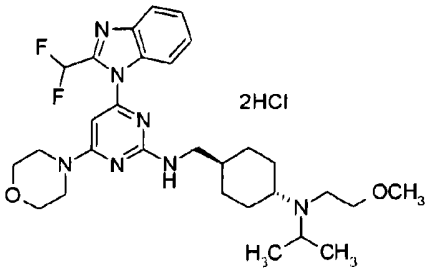
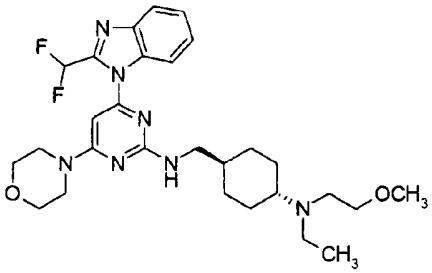
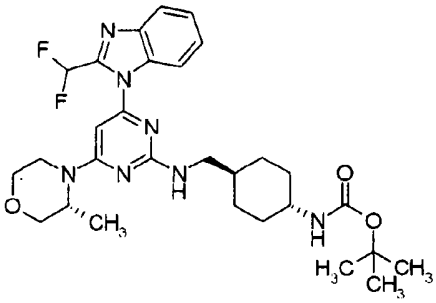
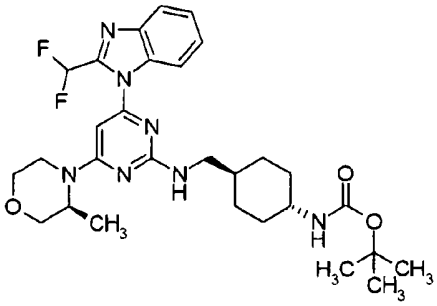
[0517]

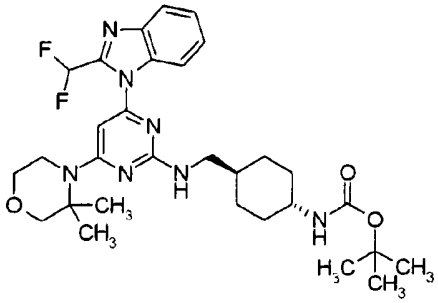
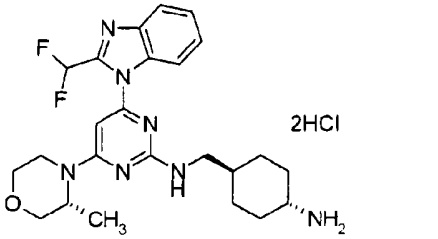
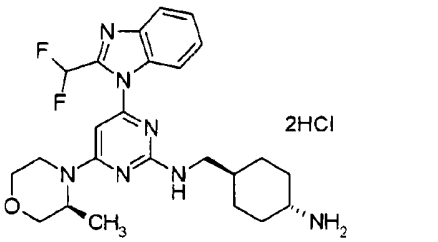
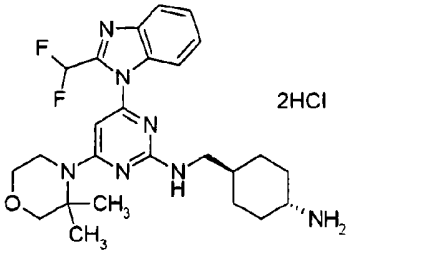
Ex	Str
354	
355	
356	
357	

Ex	Str
358	
359	
360	
361	

[0518] [表 60]

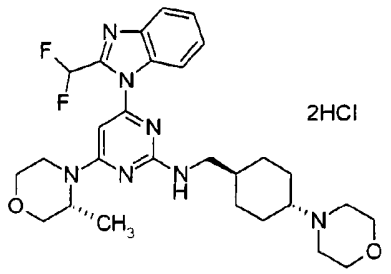
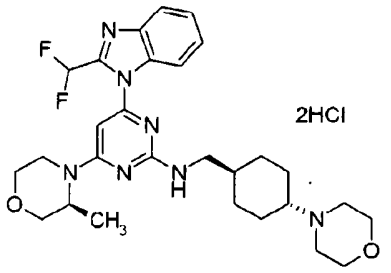
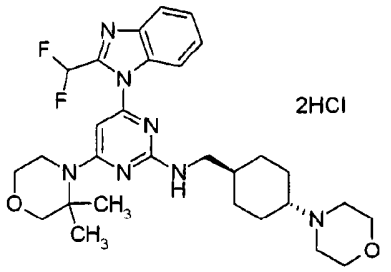
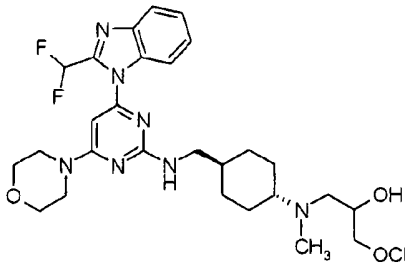
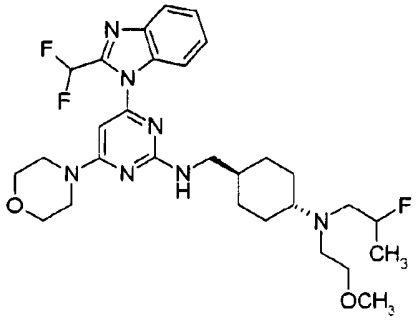
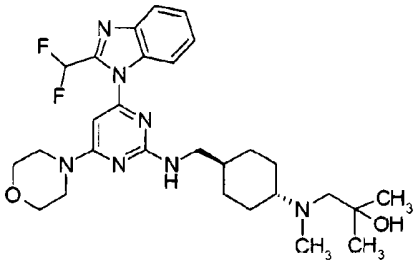
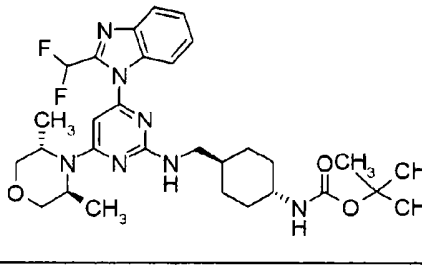
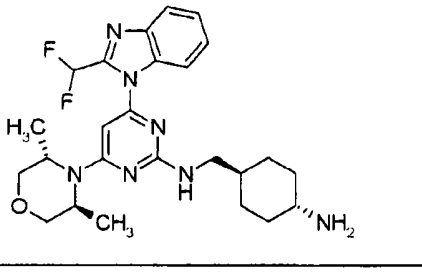
[0519]

Ex	Str
362	
363	
364	
365	

Ex	Str
366	
367	
368	
369	

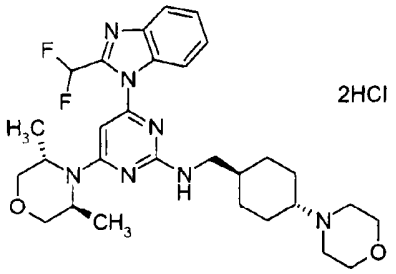
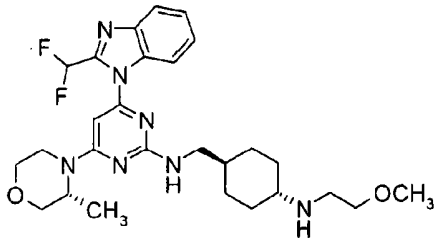
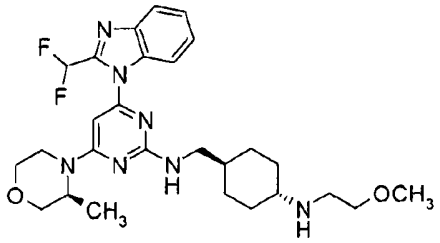
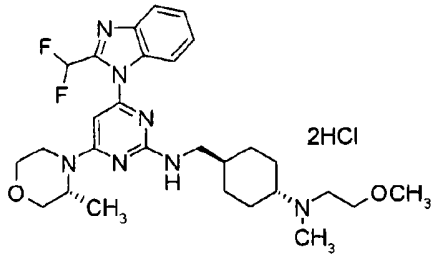
[0520] [表 61]

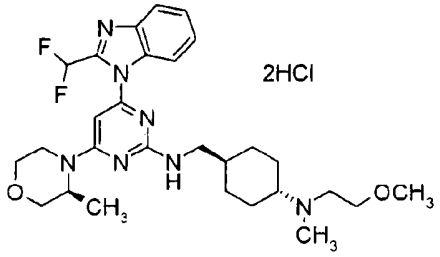
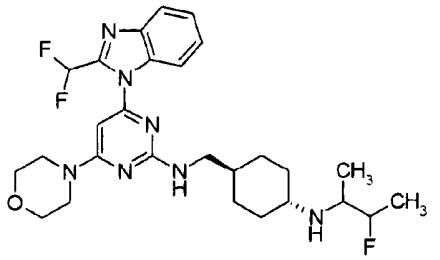
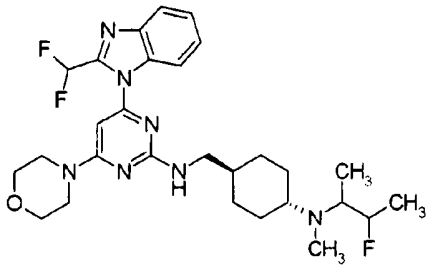
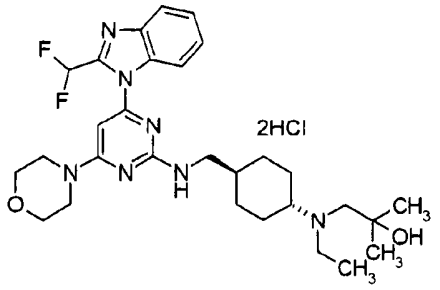
[0521]

Ex	Str
370	
371	
372	
373	
374	
375	
376	
377	

[0522] [表 62]

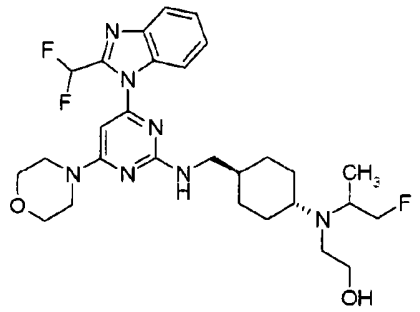
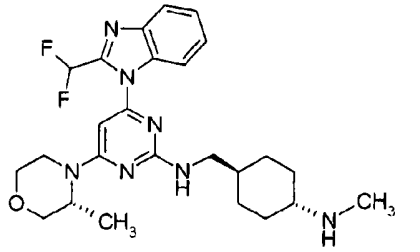
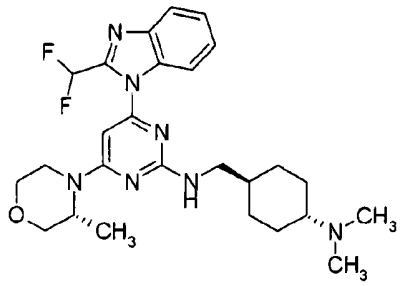
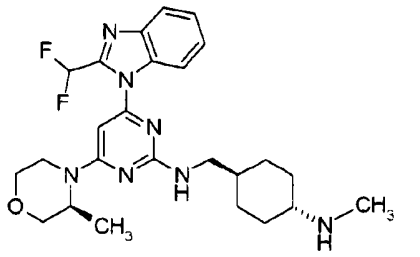
[0523]

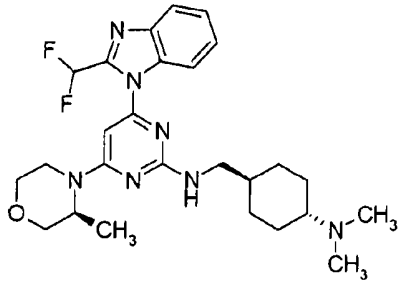
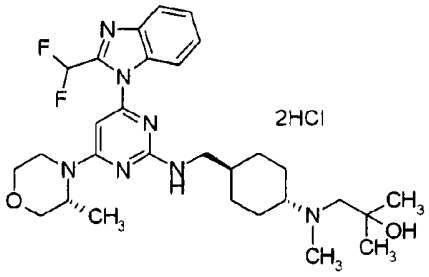
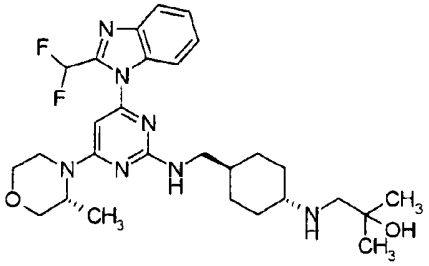
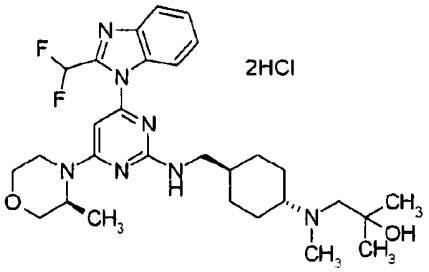
Ex	Str
378	
379	
380	
381	

Ex	Str
382	
383	
384	
385	

[0524] [表 63]

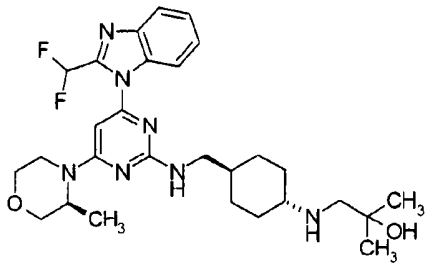
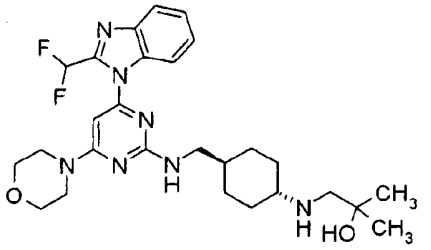
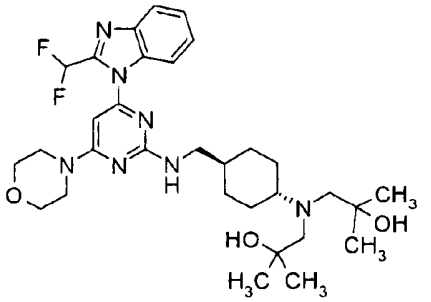
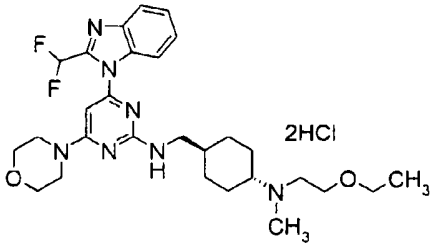
[0525]

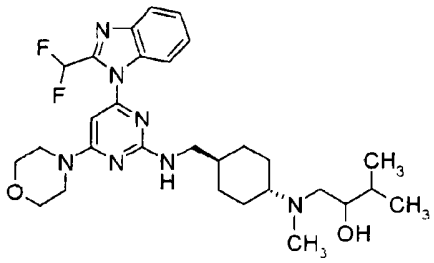
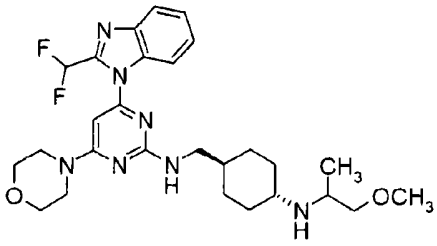
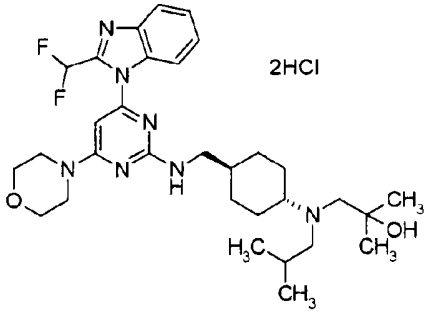
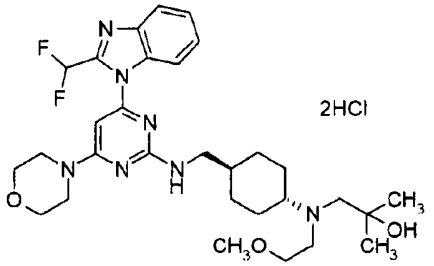
Ex	Str
386	
387	
388	
389	

Ex	Str
390	
391	
392	
393	

[0526] [表 64]

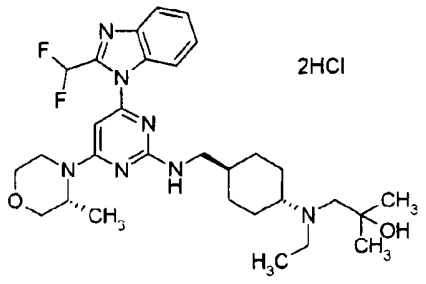
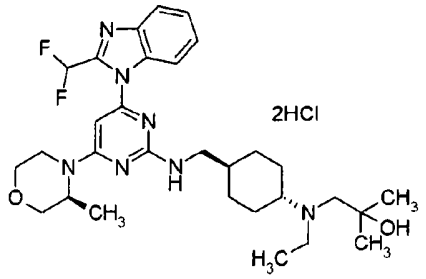
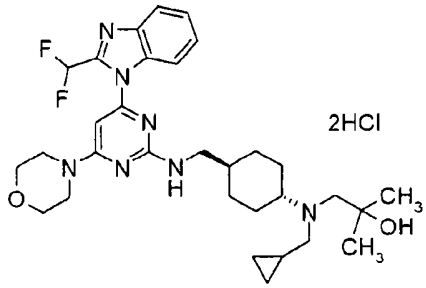
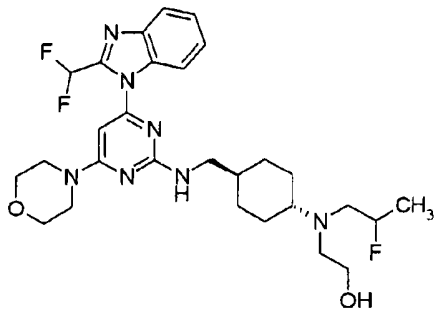
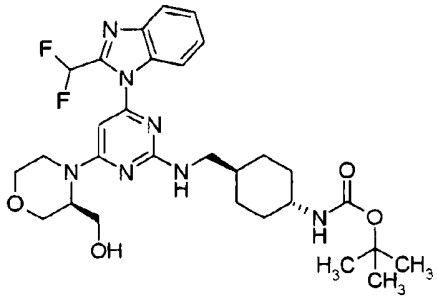
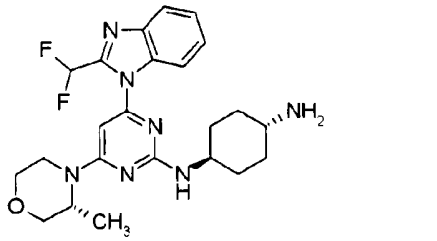
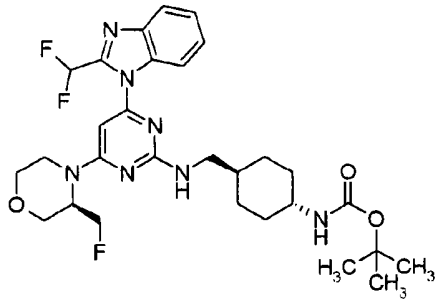
[0527]

Ex	Str
394	
395	
396	
397	

Ex	Str
398	
399	
400	
401	

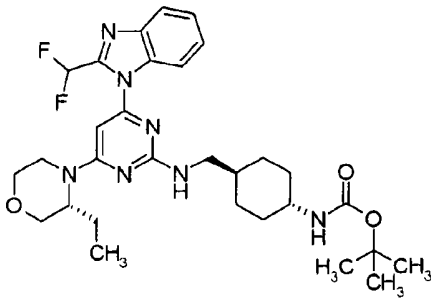
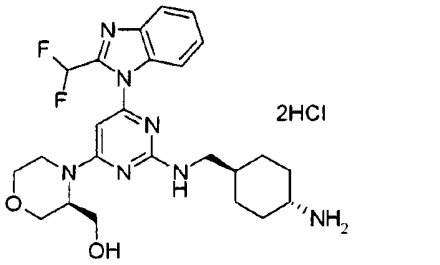
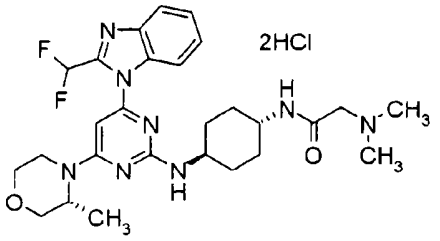
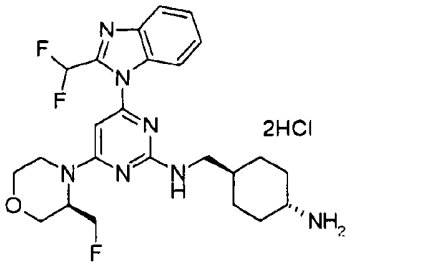
[0528] [表 65]

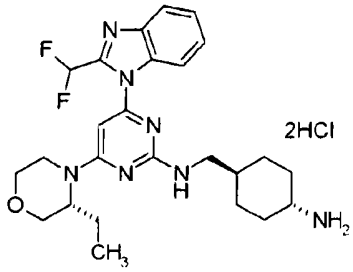
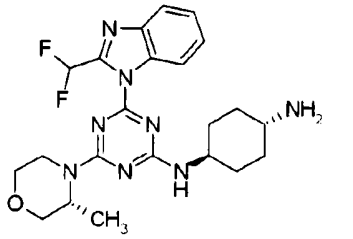
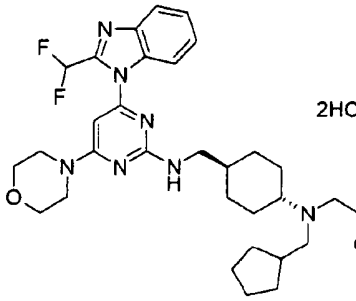
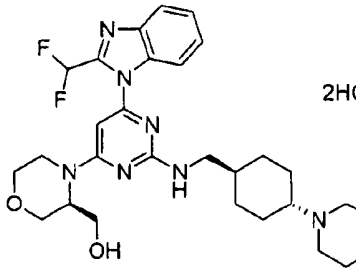
[0529]

Ex	Str
402	
403	
404	
405	
406	
407	
408	

[0530] [表 66]

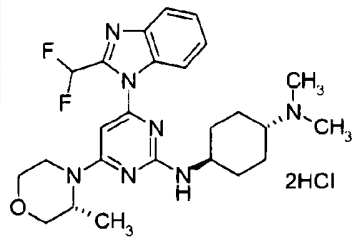
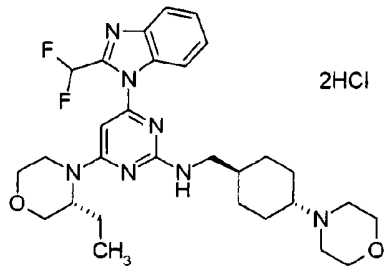
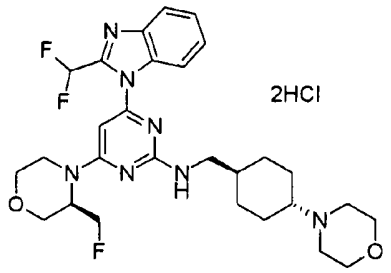
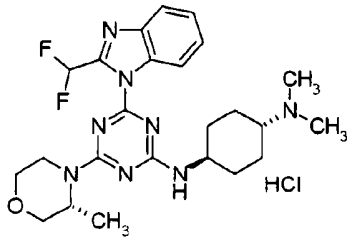
[0531]

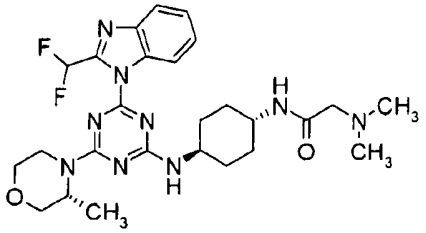
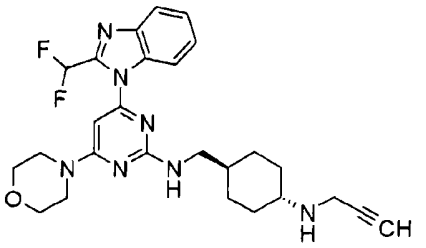
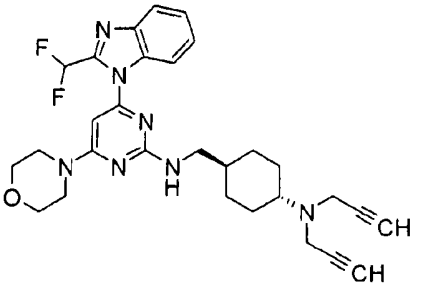
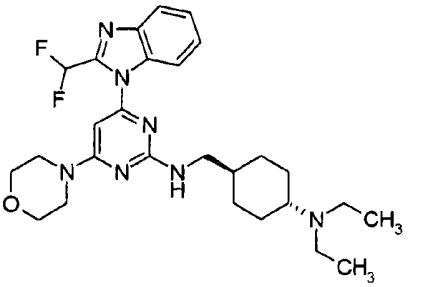
Ex	Str
409	
410	
411	
412	

Ex	Str
413	
414	
415	
416	

[0532] [表 67]

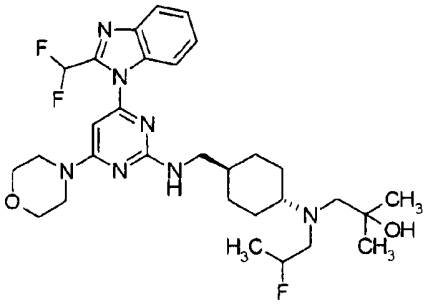
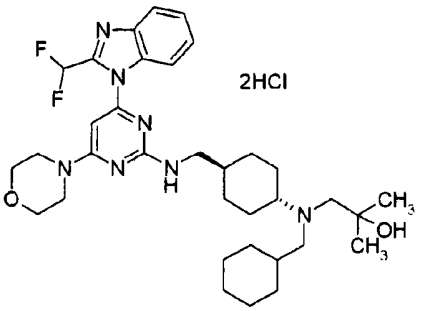
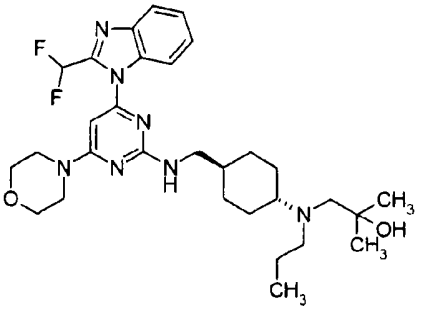
[0533]

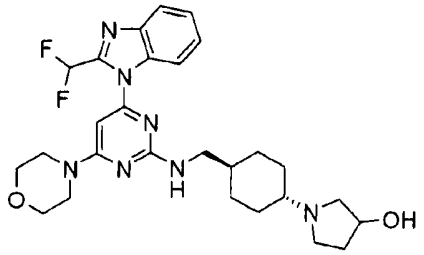
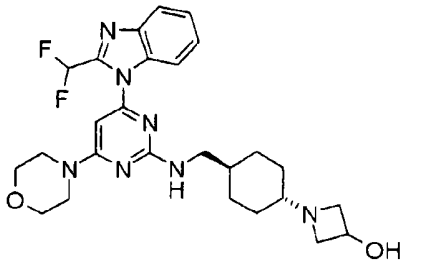
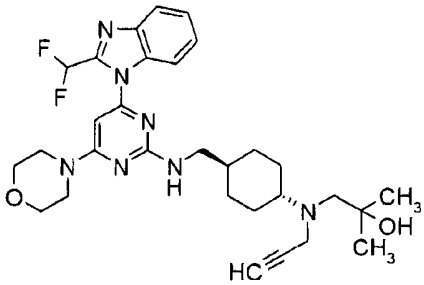
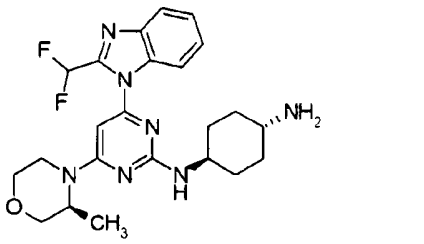
Ex	Str
417	
418	
419	
420	

Ex	Str
421	
422	
423	
424	

[0534] [表 68]

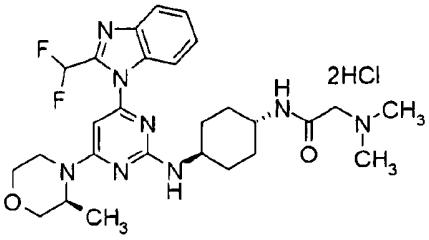
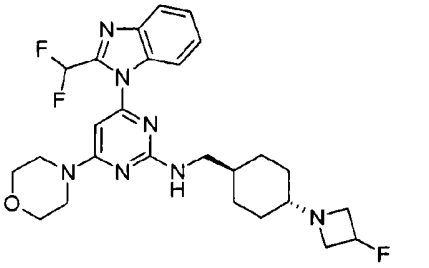
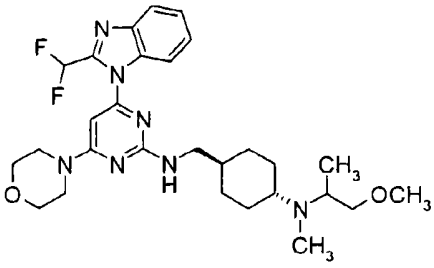
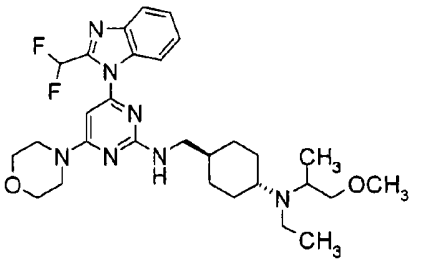
[0535]

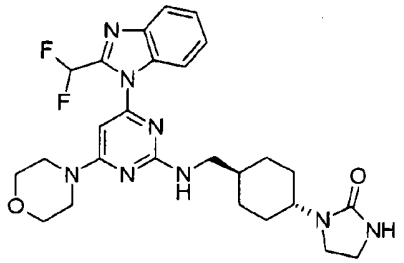
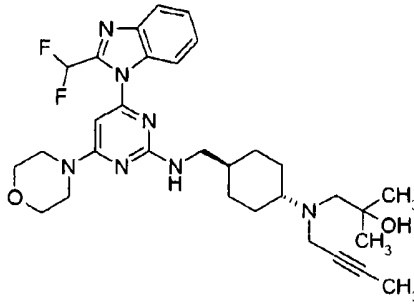
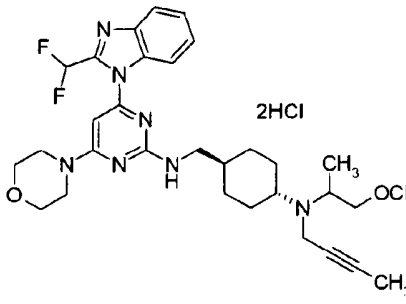
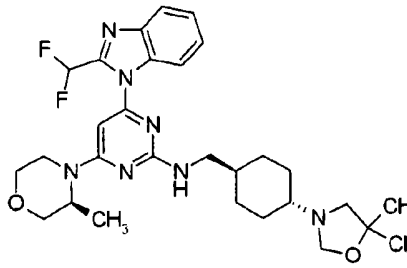
Ex	Str
425	
426	
427	

Ex	Str
428	
429	
430	
431	

[0536] [表 69]

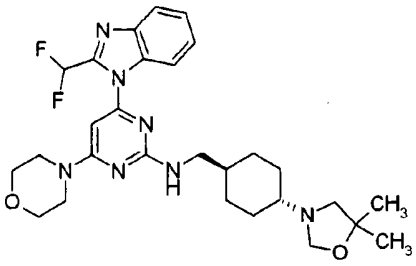
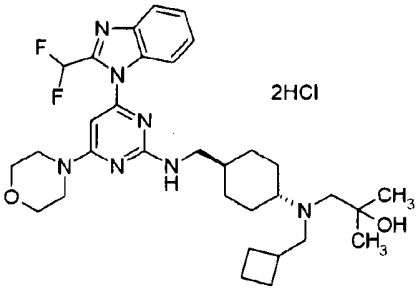
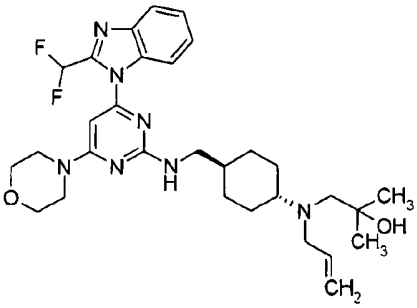
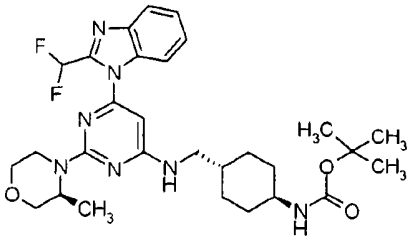
[0537]

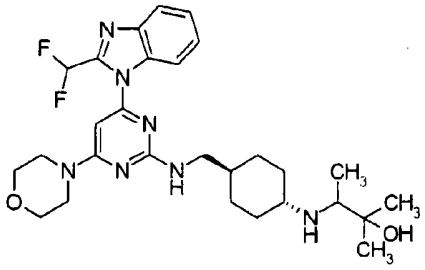
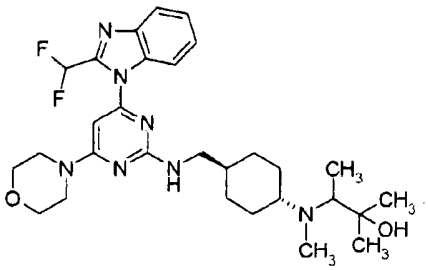
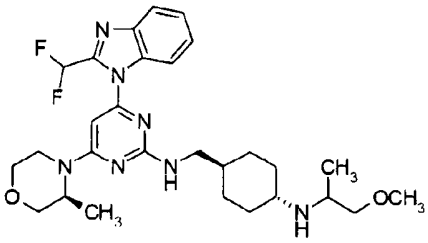
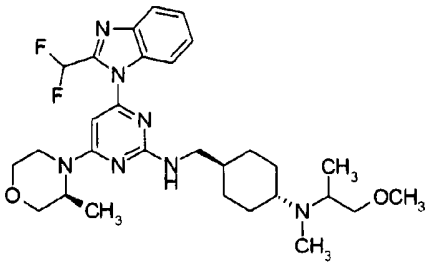
Ex	Str
432	
433	
434	
435	

Ex	Str
436	
437	
438	
439	

[0538] [表 70]

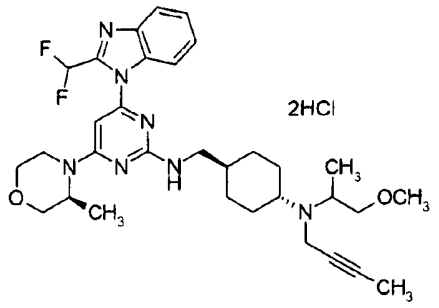
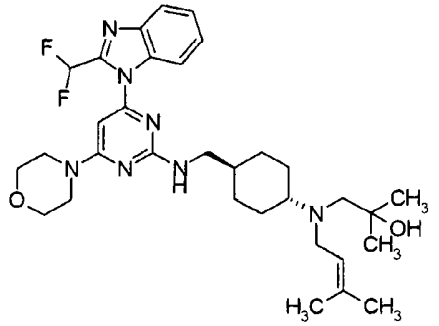
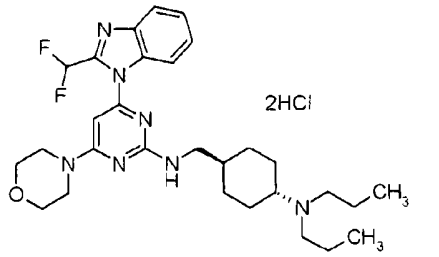
[0539]

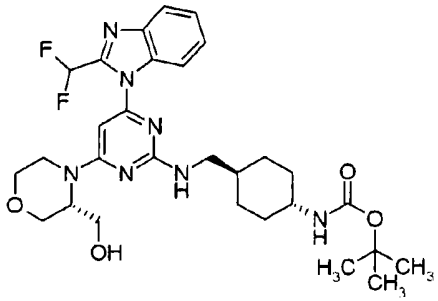
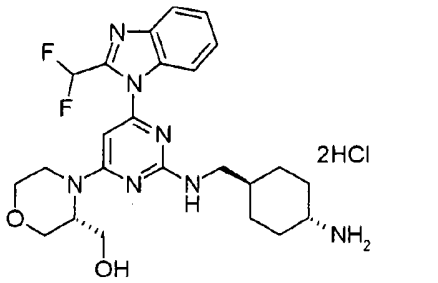
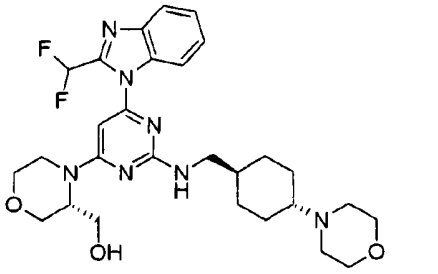
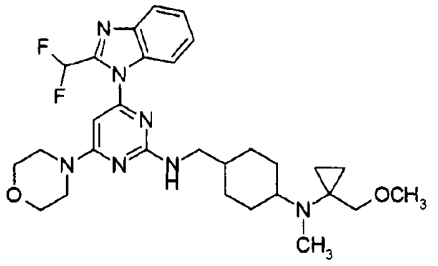
Ex	Str
440	
441	
442	
443	

Ex	Str
444	
445	
446	
447	

[0540] [表 71]

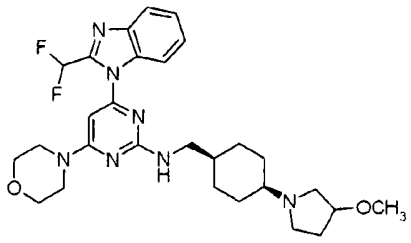
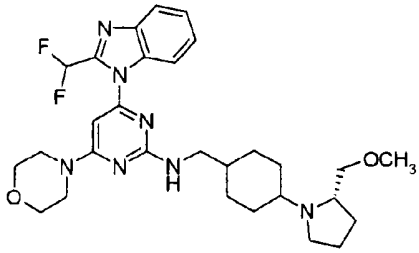
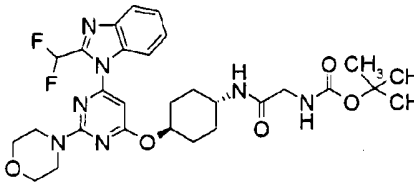
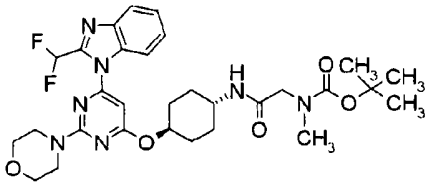
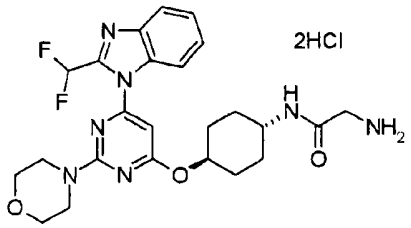
[0541]

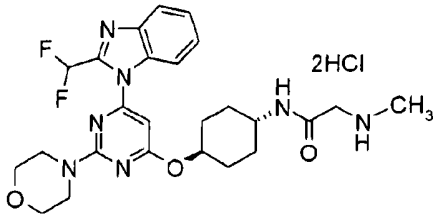
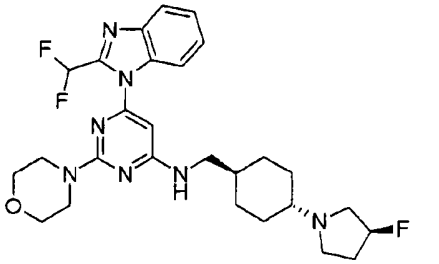
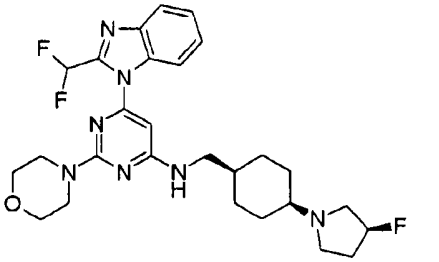
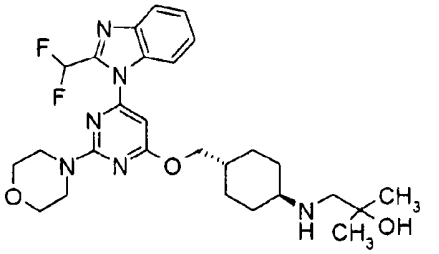
Ex	Str
448	
449	
450	

Ex	Str
451	
452	
453	
454	

[0542] [表 72]

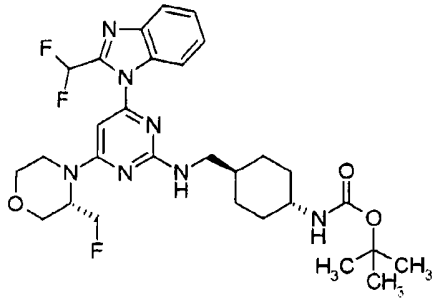
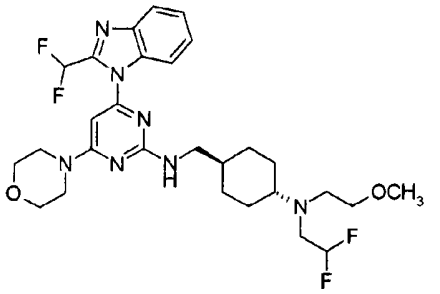
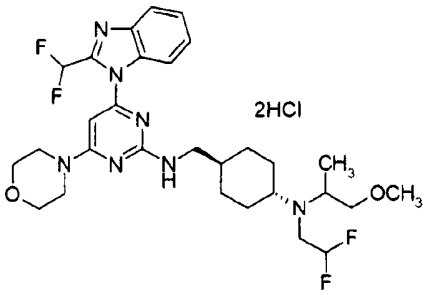
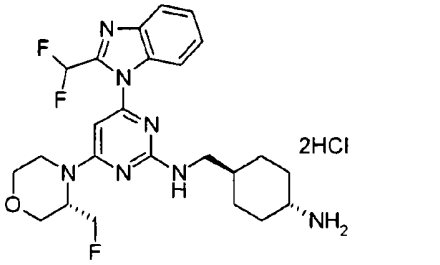
[0543]

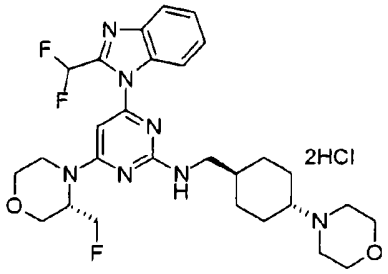
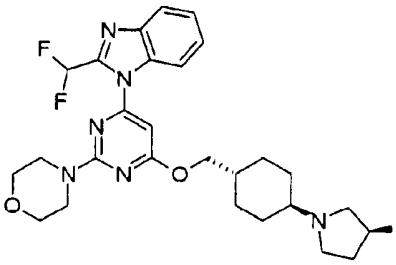
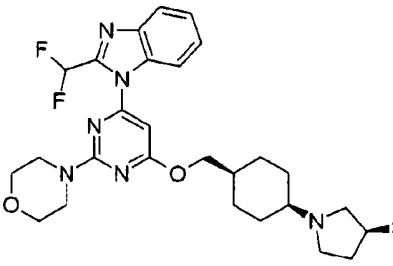
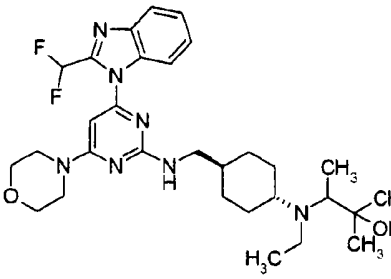
Ex	Str
455	
456	
457	
458	
459	

Ex	Str
460	
461	
462	
463	

[0544] [表 73]

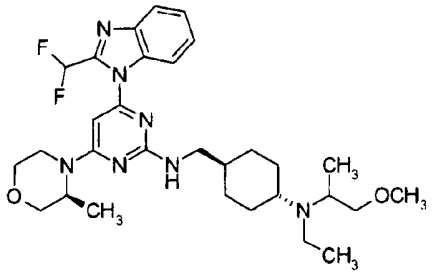
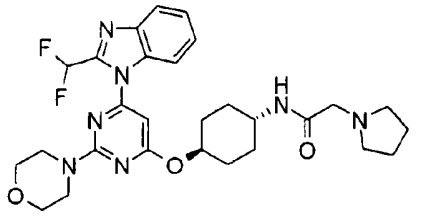
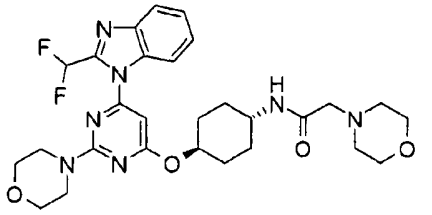
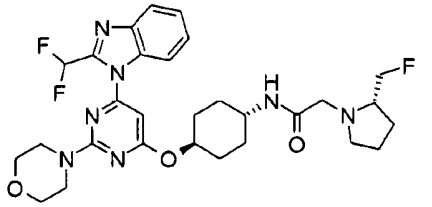
[0545]

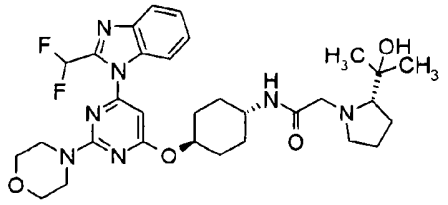
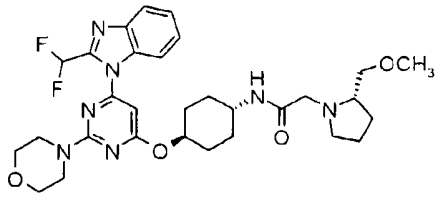
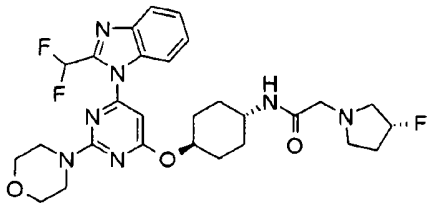
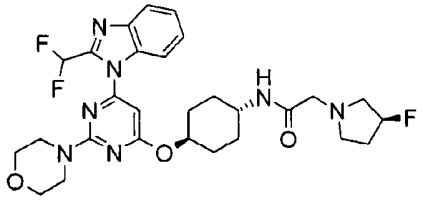
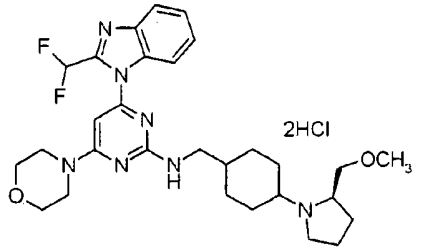
Ex	Str
464	
465	
466	
467	

Ex	Str
468	
469	
470	
471	

[0546] [表 74]

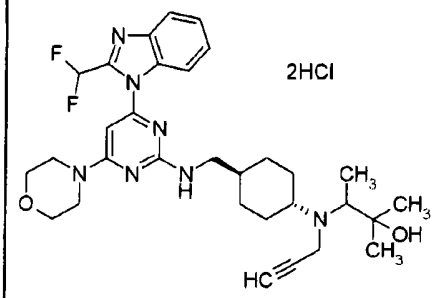
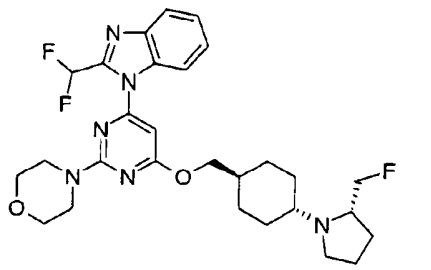
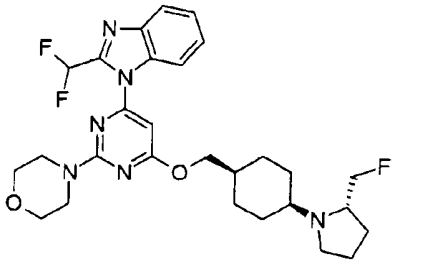
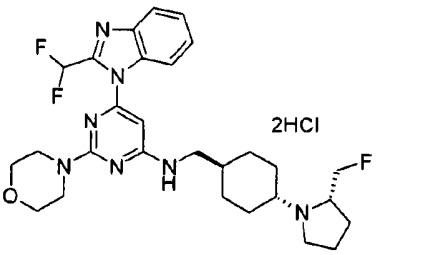
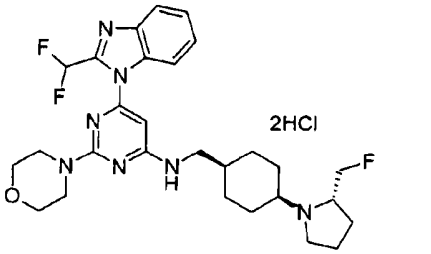
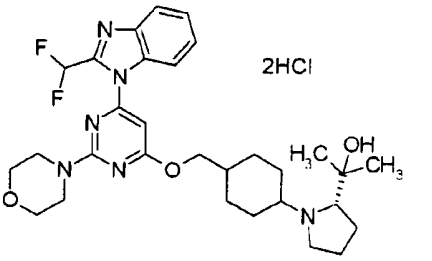
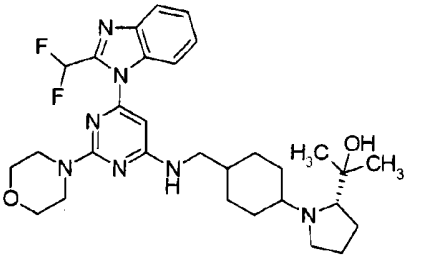
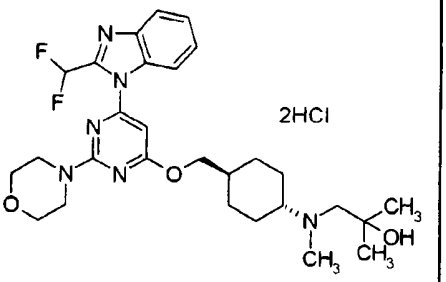
[0547]

Ex	Str
472	
473	
474	
475	

Ex	Str
476	
477	
478	
479	
480	

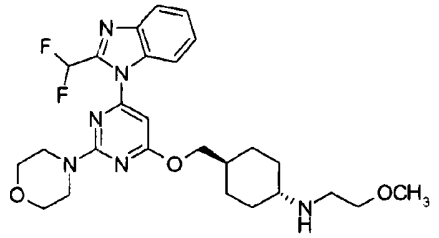
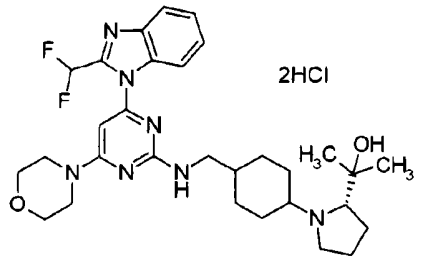
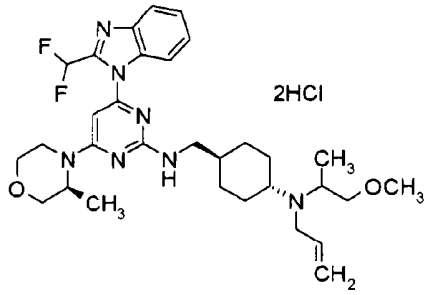
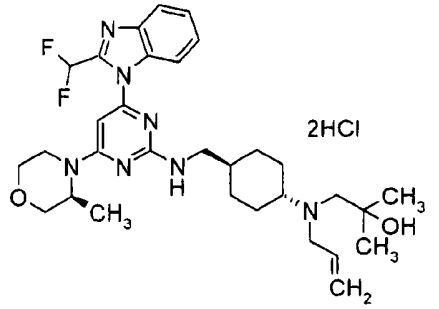
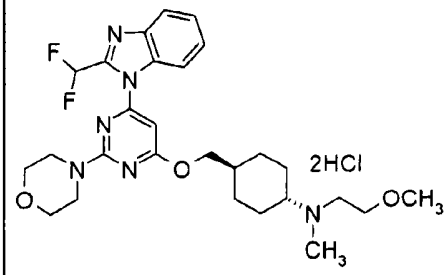
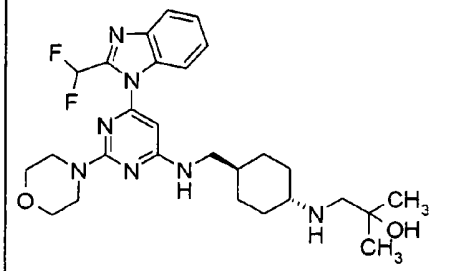
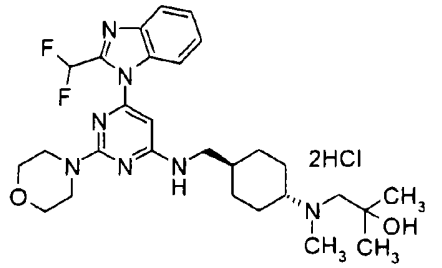
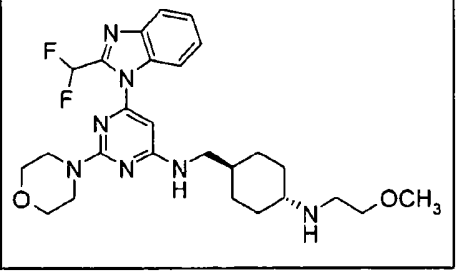
[0548] [表 75]

[0549]

Ex	Str
481	
482	
483	
484	
485	
486	
487	
488	

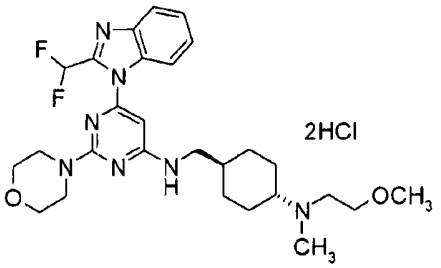
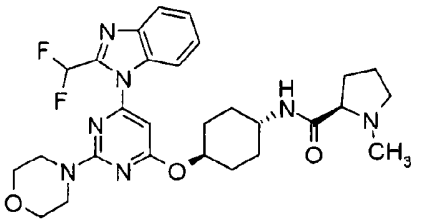
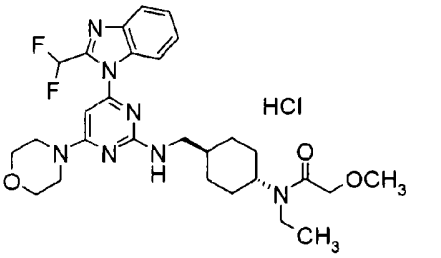
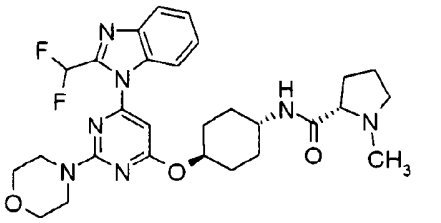
[0550] [表 76]

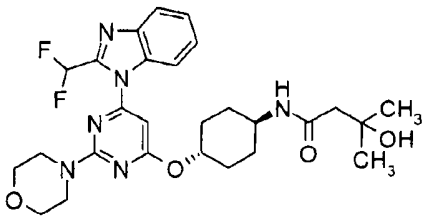
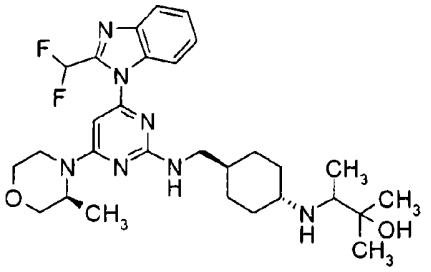
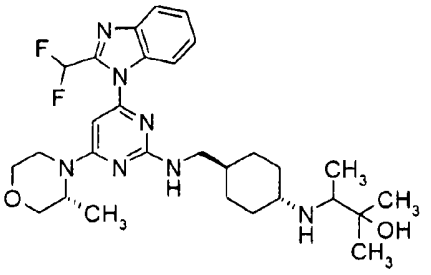
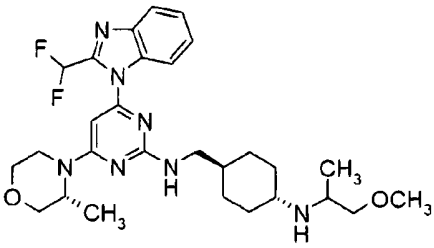
[0551]

Ex	Str
489	
490	
491	
492	
493	
494	
495	
496	

[0552] [表 77]

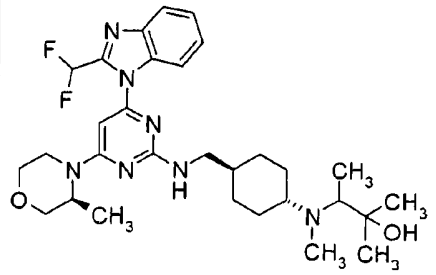
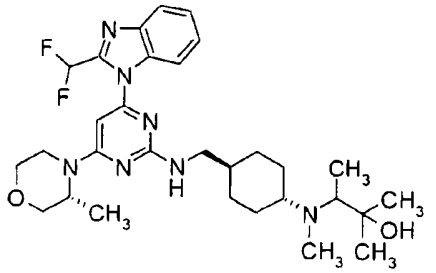
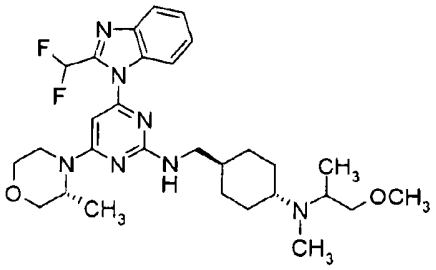
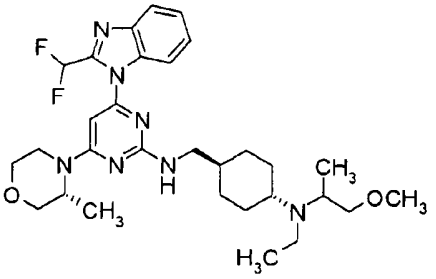
[0553]

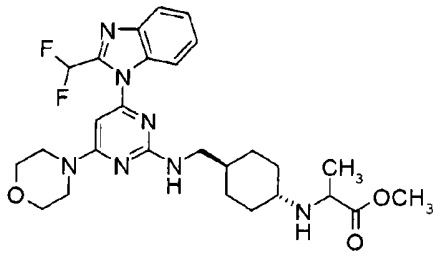
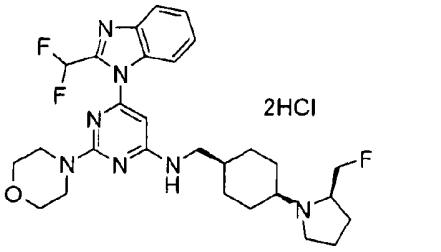
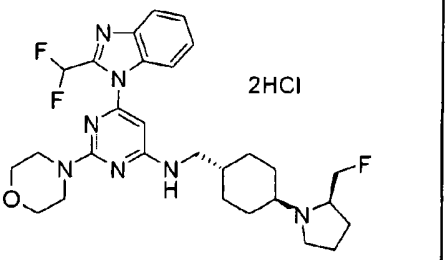
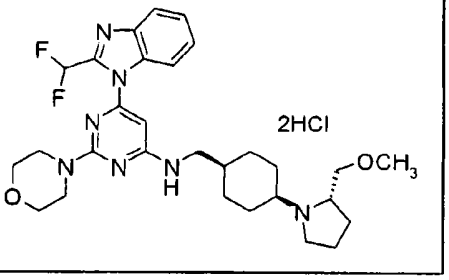
Ex	Str
497	
498	
499	
500	

Ex	Str
501	
502	
503	
504	

[0554] [表 78]

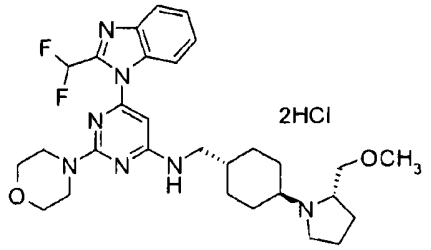
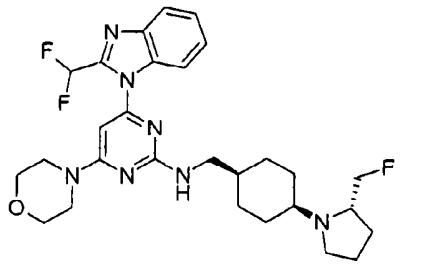
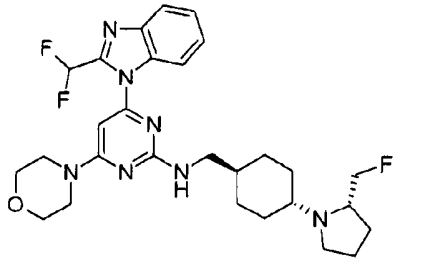
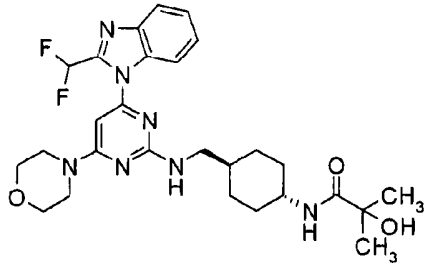
[0555]

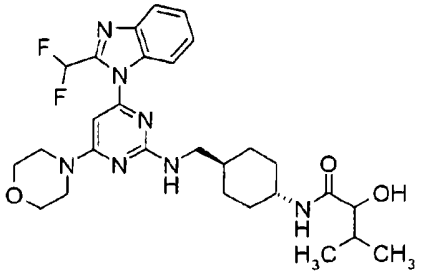
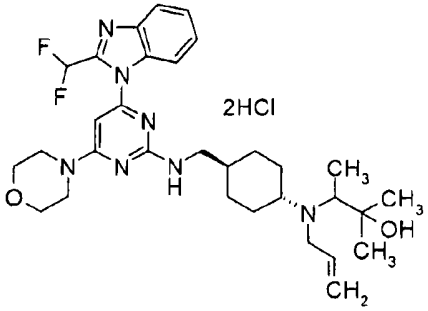
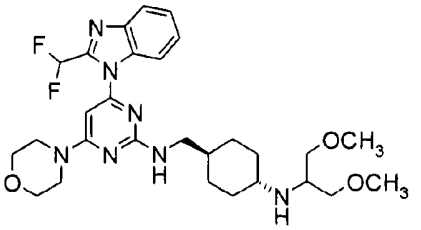
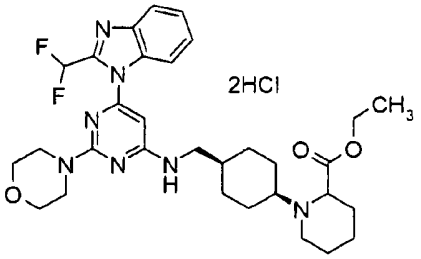
Ex	Str
505	
506	
507	
508	

Ex	Str
509	
510	
511	
512	

[0556] [表 79]

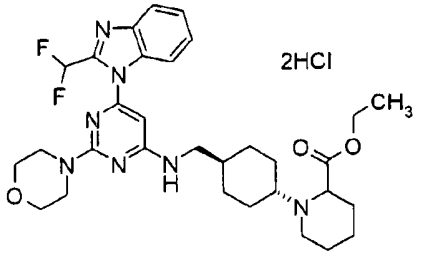
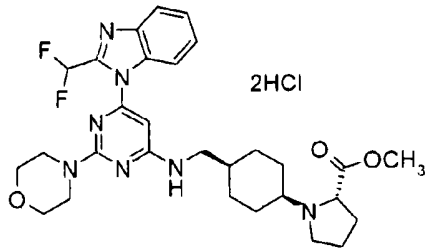
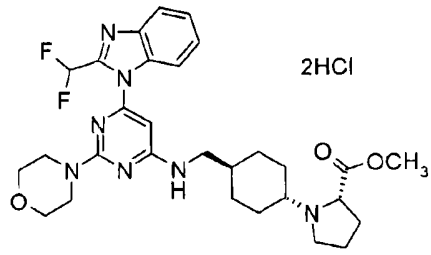
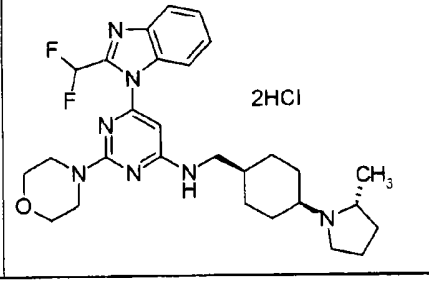
[0557]

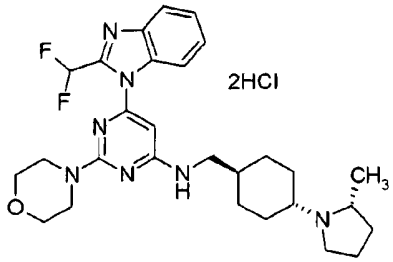
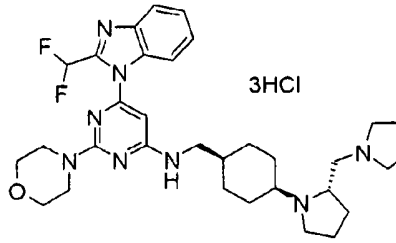
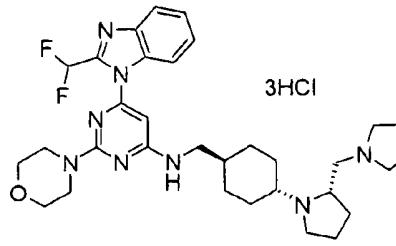
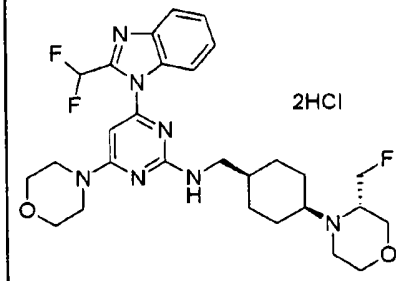
Ex	Str
513	
514	
515	
516	

Ex	Str
517	
518	
519	
520	

[0558] [表 80]

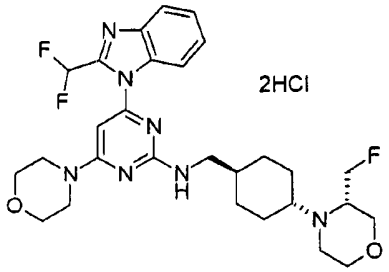
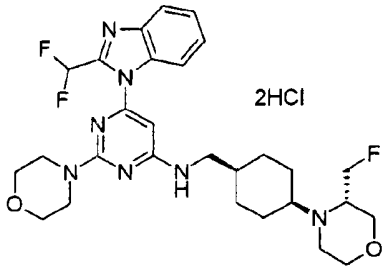
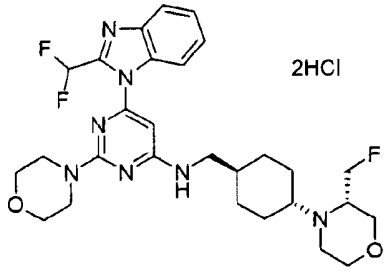
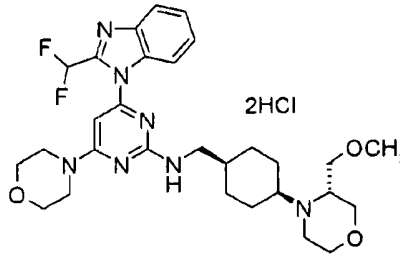
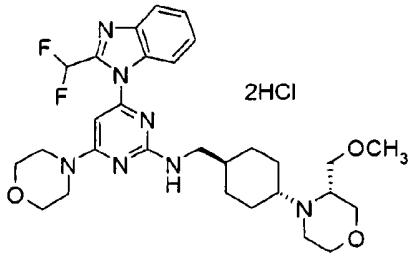
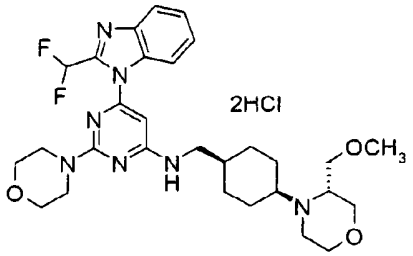
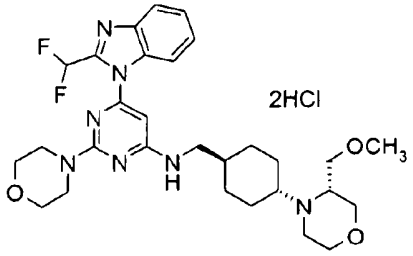
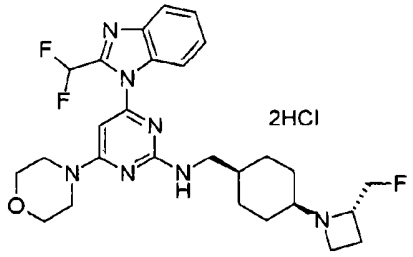
[0559]

Ex	Str
521	
522	
523	
524	

Ex	Str
525	
526	
527	
528	

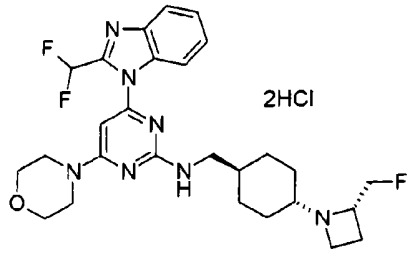
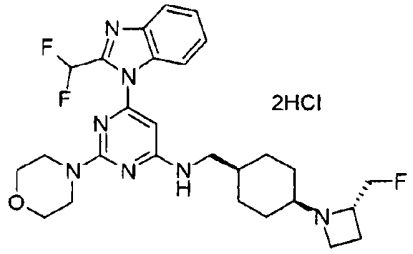
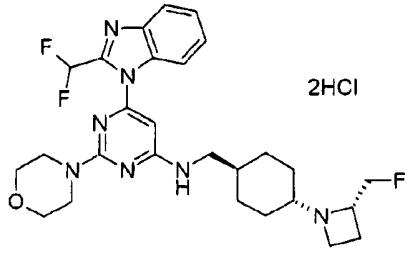
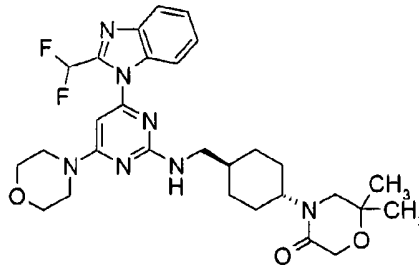
[0560] [表 81]

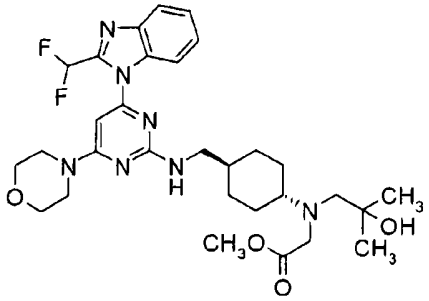
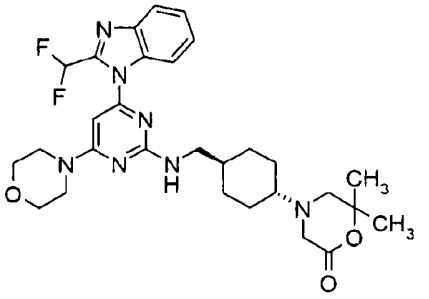
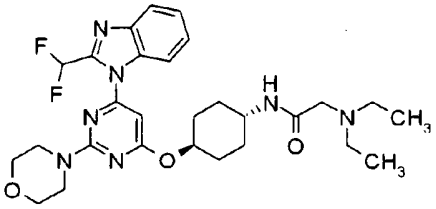
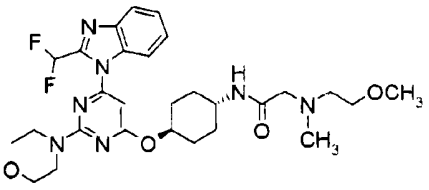
[0561]

Ex	Str
529	
530	
531	
532	
533	
534	
535	
536	

[0562] [表 82]

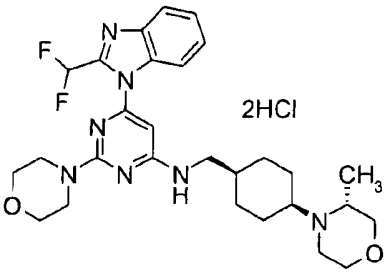
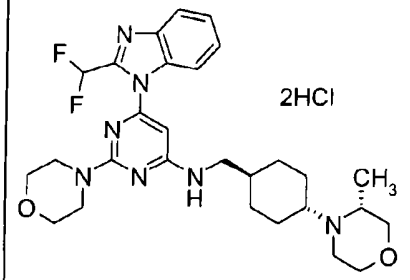
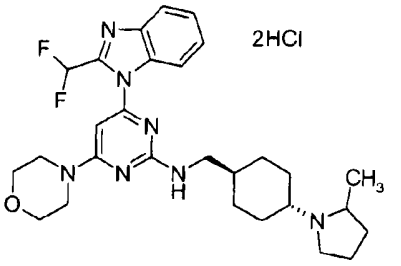
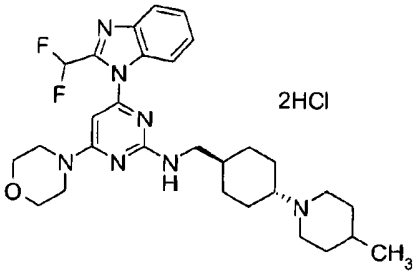
[0563]

Ex	Str
537	
538	
539	
540	

Ex	Str
541	
542	
543	
544	

[0564] [表 83]

[0565]

Ex	Str
545	
546	
547	
548	

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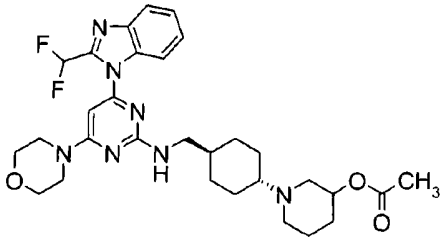
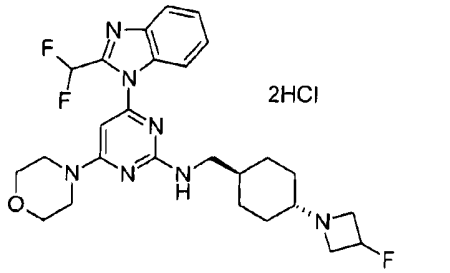
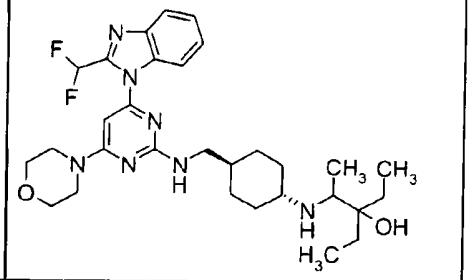
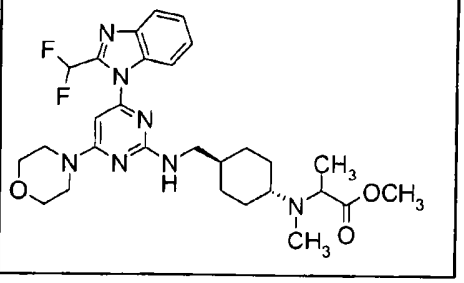
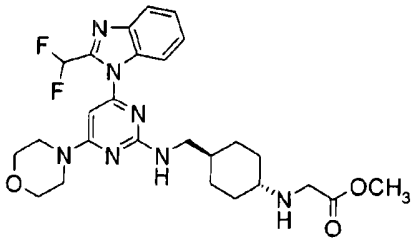
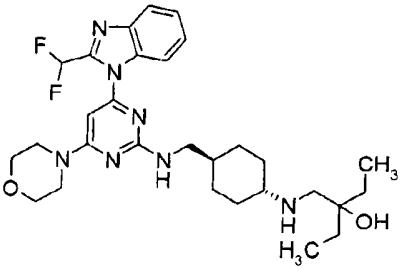
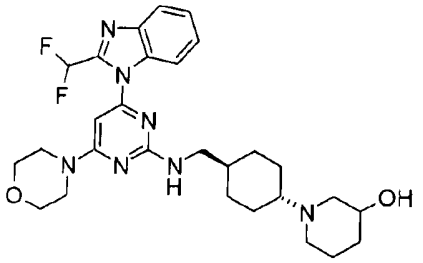
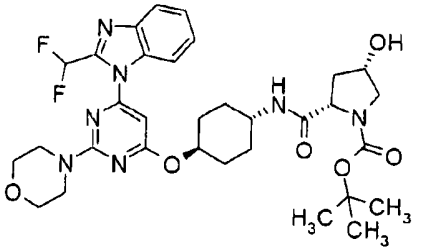
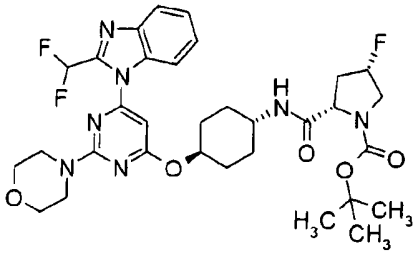
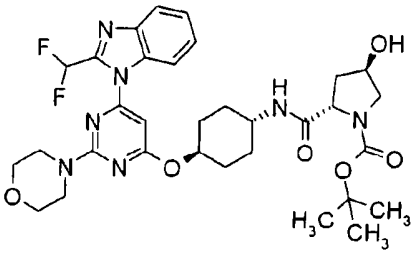
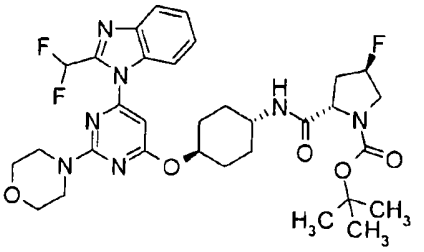
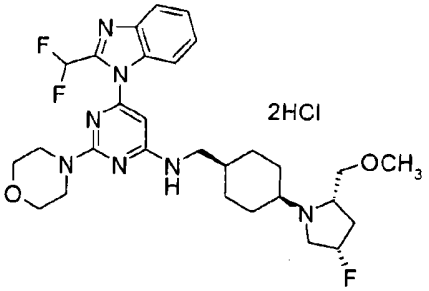
549	
550	
551	
552	

[0566] [表 84]

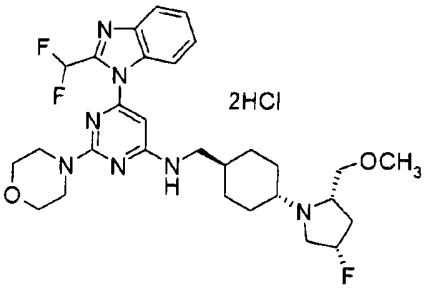
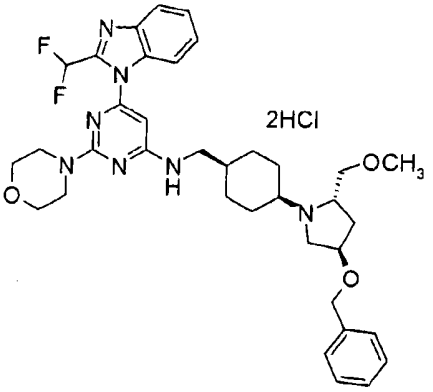
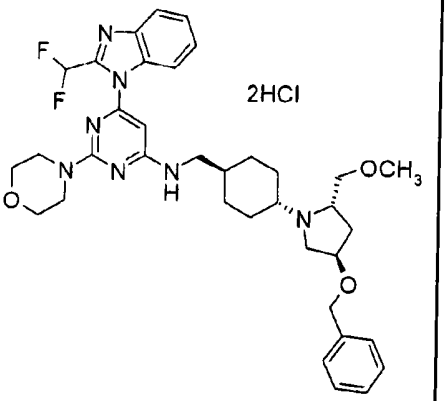
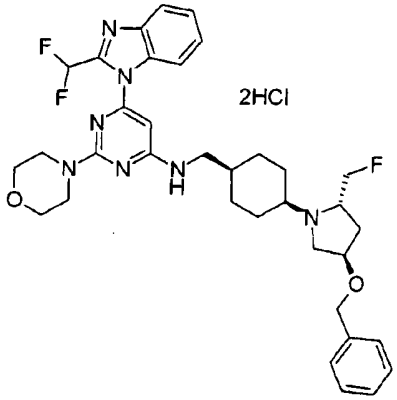
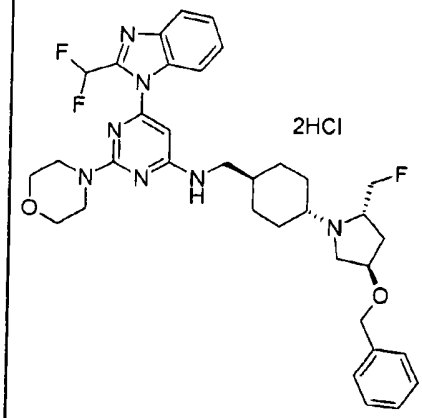
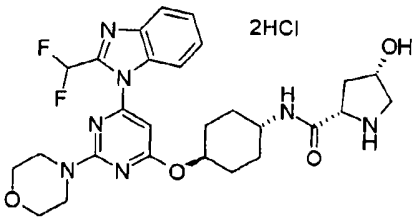
[0567]

Ex	Str
553	
554	
555	
556	

Ex	Str
557	
558	
559	
560	

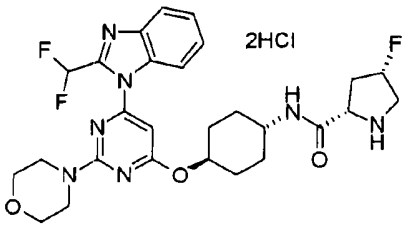
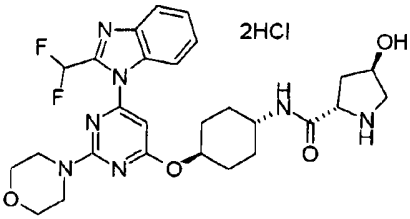
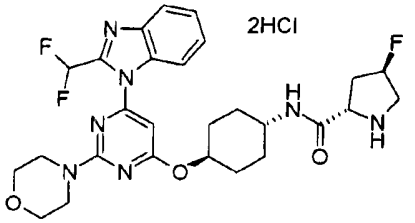
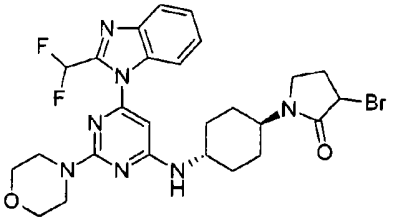
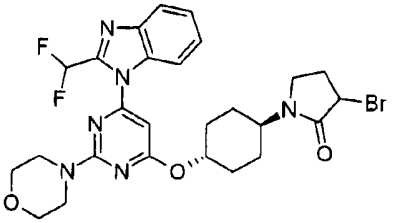
[0568] [表 85]

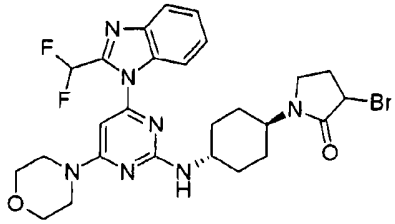
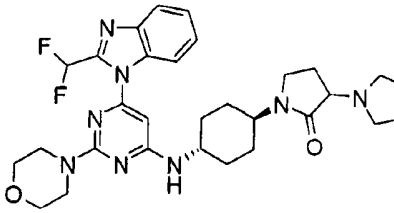
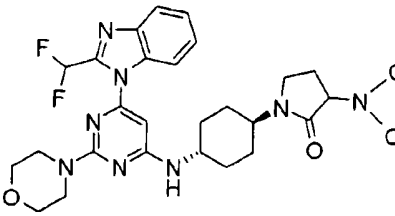
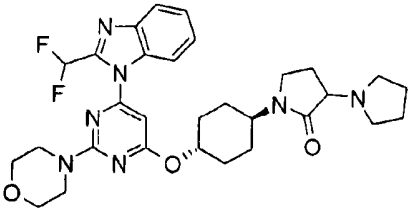
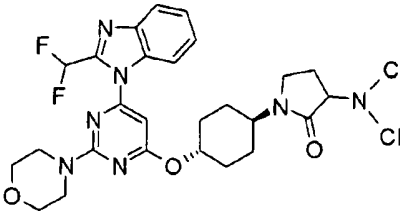
[0569]

Ex	Str
561	
562	
563	
564	
565	
566	

[0570] [表 86]

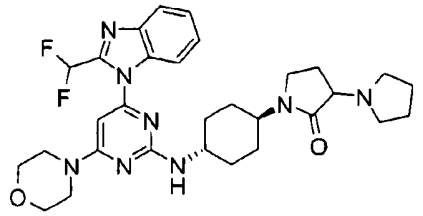
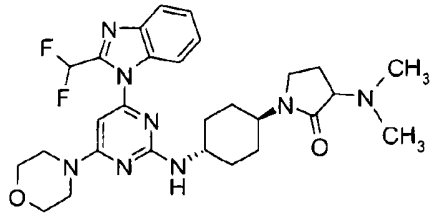
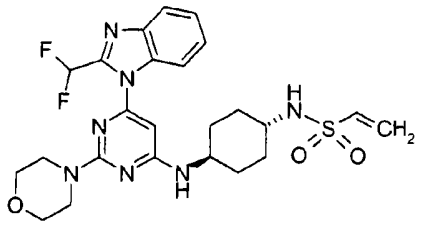
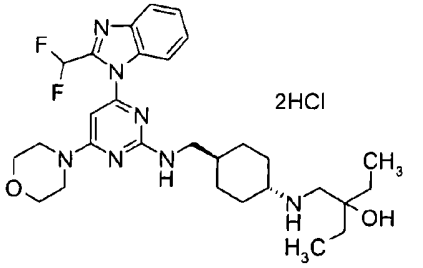
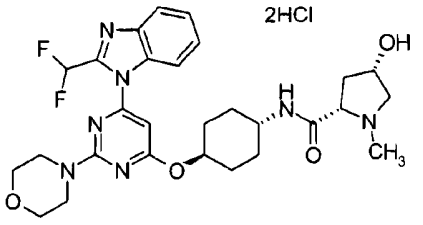
[0571]

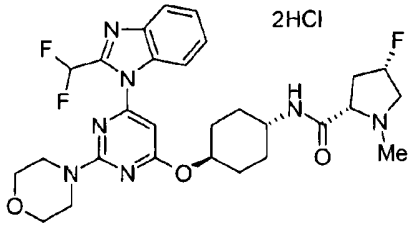
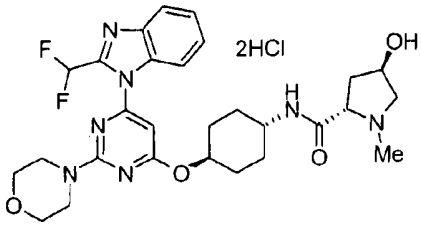
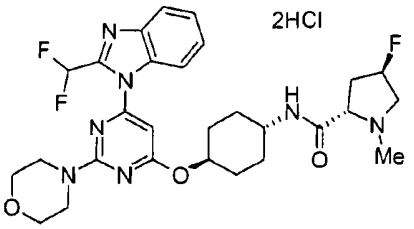
Ex	Str
567	
568	
569	
570	
571	

Ex	Str
572	
573	
574	
575	
576	

[0572] [表 87]

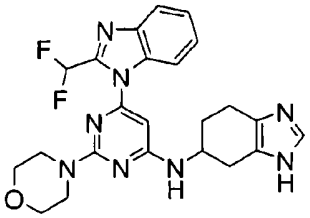
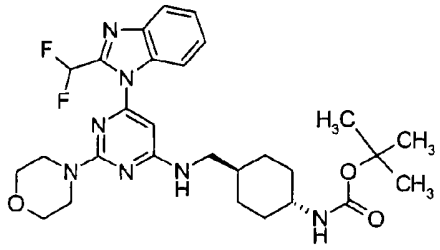
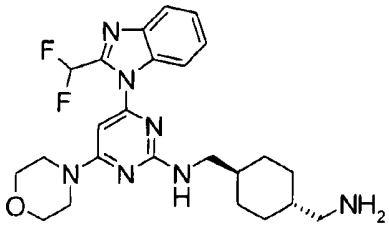
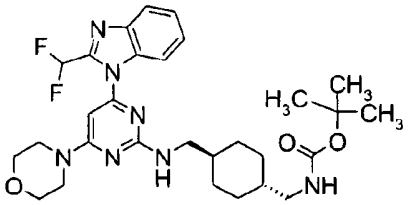
[0573]

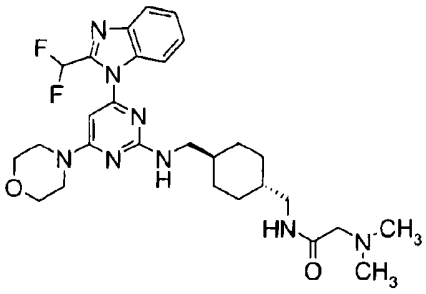
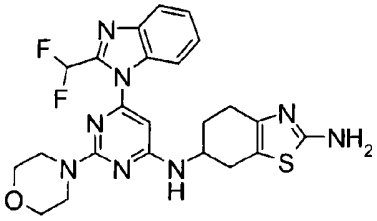
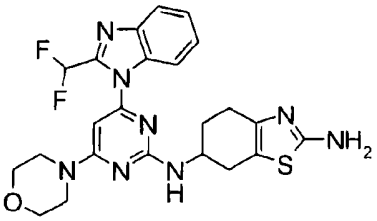
Ex	Str
577	
578	
579	
580	
581	

Ex	Str
582	
583	
584	

[0574] [表 88]

[0575]

Ex	Str
585	
586	
587	
588	

Ex	Str
589	
590	
591	

[0576] [表 89]

[0577]

Ex	Syn	DATA
1	1	ESI+: 444 NMR1: 0.95-2.02 (11H, m), 3.55-3.77 (9H, m), 6.23-6.39 (1H, m), 6.84-7.04 (1H, m), 7.35-7.90 (5H, m)
2	2	ESI+: 517 NMR1: 1.32-1.51 (4H, m), 1.70-2.03 (4H, m), 2.29-2.30 (3H, m), 3.55-3.86 (10H, m), 3.78 (2H, s), 7.40-7.69 (3H, m), 7.78-8.05 (3H, m), 8.42-8.59 (1H, m)
3	3	ESI+: 551 NMR1: 0.96-1.00 (3H, m), 1.29-1.43 (4H, m), 1.61-1.72 (2H, m), 1.87-2.01 (4H, m), 2.96-3.01 (2H, m), 3.05-3.15 (1H, m), 3.65-3.83 (9H, m), 7.02-7.06 (1H, m), 7.40-7.49 (2H, m), 7.64-8.05 (3H, m), 8.41-8.58 (1H, m)
4	4	ESI+: 473 NMR1: 1.22-1.40 (4H, m), 1.79-2.21 (10H, m), 3.64-3.85 (9H, m), 7.38-7.52 (2H, m), 7.63-8.07 (3H, m), 8.40-8.69 (1H, m)
5	5	ESI+: 524 [M+Na] NMR1: 1.18-123 (2H, m), 1.31-1.44 (2H, m), 1.85-1.99 (4H, m), 2.53-2.54 (3H, m), 3.70-3.78 (9H, m), 5.54-5.82 (2H, m), 7.42-7.49 (2H, m), 7.64-7.92 (3H, m), 8.41-8.58 (1H, m)
6	6	ESI+: 601 NMR1: 1.15-1.25 (2H, m), 1.33-1.42 (2H, m), 1.84-1.99 (4H, m), 2.29-2.37 (6H, m), 3.08-3.12 (2H, m), 3.56-3.58 (4H, m), 3.67-3.83 (8H, m), 5.58-5.66 (1H, m), 5.87-5.99 (1H, m), 7.40-7.51 (2H, m), 7.65-8.05 (3H, m), 8.41-8.58 (1H, m)
7	7	ESI+: 545 NMR1: 1.22-1.42 (13H, m), 1.77-2.01 (4H, m), 3.14-3.32 (1H, m), 3.60-3.83 (9H, m), 6.75-6.79 (1H, m), 7.40-7.51 (2H, m), 7.63-8.05 (3H, m), 8.41-8.58 (1H, m)
8	8	ESI+: 502 NMR1: 1.23-1.45 (4H, m), 1.72-2.01 (6H, m), 3.04 (2H, s), 3.48-3.85 (10H, m), 7.38-8.05 (6H, m), 8.42-8.60 (1H, m)

[0578] [表 90]

[0579]

Ex	Syn	DATA
9	9	ESI+: 565, 567 NMR1: 1.21-1.47 (4H, m), 1.82-2.04 (4H, m), 3.45-3.85 (12H, m), 7.39-7.51 (2H, m), 7.65-8.05 (4H, m), 8.42-8.59 (1H, m)
10	10	ESI+: 515 NMR1: 1.23-1.40 (4H, m), 1.81-2.06 (4H, m), 2.13-2.26 (1H, m), 2.45-2.51 (4H, m), 3.53-3.60 (4H, m), 3.65-3.87 (9H, m), 7.39-7.54 (2H, m), 7.63-8.07 (3H, m), 8.39-8.60 (1H, m)
11	11	ESI+: 534 [M+Na]
12	12	ESI+: 556 NMR1: 1.36-1.47 (4H, m), 1.67-1.84 (6H, m), 1.92-2.01 (2H, m), 2.45-2.62 (4H, m), 3.01-3.02 (2H, m), 3.54-3.82 (10H, m), 7.40-7.64 (3H, m), 7.78-8.05 (3H, m), 8.41-8.56 (1H, m)
13	13	ESI+: 570 [M+Na] NMR1: 1.27-1.43 (2H, m), 1.47-1.69 (2H, m), 1.72-2.10 (4H, m), 2.13-2.26 (2H, m), 3.09-3.28 (4H, m), 3.58-3.75 (9H, m), 6.26-6.40 (1H, m), 6.90-7.06 (1H, m), 7.36-7.96 (5H, m)
14	14	ESI+: 501 NMR1: 1.33-1.75 (6H, m), 1.95-2.06 (5H, m), 2.70-2.83 (3H, m), 3.55-4.33 (10H, m), 7.40-7.53 (2H, m), 7.66-8.05 (3H, m), 8.42-8.58 (1H, m)
15	15	ESI+: 459 NMR1: 1.03-1.57 (5H, m), 1.89-2.00 (4H, m), 2.17-2.45 (1H, m), 2.27 (3H, t, J = 0.8 Hz), 3.62-3.85 (9H, m), 7.40-7.51 (2H, m), 7.64-8.06 (3H, m), 8.41-8.58 (1H, m)
16	16	ESI+: 529 NMR1: 1.24-1.43 (4H, m), 1.80-2.09 (4H, m), 2.79 (3H, s), 2.81 (3H, s), 3.44-3.67 (9H, m), 3.78-3.95 (3H, m), 6.12 (1H, s), 7.39-7.65 (4H, m), 7.72 (1H, d, J = 8.1 Hz), 7.86 (1H, d, J = 7.7 Hz), 8.59 (1H, d, J = 7.1 Hz), 9.81 (1H, br-s)

[0580] [表 91]

[0581]

Ex	Syn	DATA
17	17	ESI+: 569 NMR1: 1.11-1.41 (4H, m), 1.59-2.03 (8H, m), 2.16-2.62 (8H, m), 3.40-3.73 (10H, m), 6.28-6.39 (1H, m), 6.90-7.06 (1H, m), 7.39-7.87 (5H, m), 8.62 (1H, s)
18	18	ESI+: 570 [M+Na]
19	19	ESI+: 667 [M+Na]
20	20	ESI+: 651 [M+Na]
21	21	ESI+: 569
22	22	ESI+: 544
23	23	ESI+: 515
24	24	ESI+: 530 NMR1: 1.36-1.50 (2H, m), 1.51-1.66 (2H, m), 1.88-1.98 (2H, m), 2.11-2.21 (2H, m), 2.79 (6H, s), 3.66-3.77 (9H, m), 3.86 (2H, s), 5.02-5.12 (1H, m), 6.41 (1H, s), 7.40-7.50 (2H, m), 7.54 (1H, t), 7.72-7.76 (1H, m), 7.85-7.89 (1H, m), 8.51-8.57 (1H, m), 9.75 (1H, br-s)
25	25	ESI+: 599 [M+Na] NMR1: 1.10-1.28 (2H, m), 1.46-1.64 (2H, m), 1.71-1.83 (1H, m), 1.90-2.02 (2H, m), 2.09-2.25 (2H, m), 3.43-3.98 (17H, m), 4.24 (2H, d), 6.43 (1H, s), 7.40-7.50 (2H, m), 7.54 (1H, t), 7.74-7.79 (1H, m), 7.85-7.89 (1H, m), 11.63 (1H, br-s)
26	26	ESI+: 518 NMR1: 0.83-1.01 (2H, m), 1.09-1.27 (2H, m), 1.38-1.54 (1H, m), 1.67-1.86 (4H, m), 2.17-2.22 (3H, m), 2.27-2.36 (1H, m), 2.60-2.72 (2H, m), 3.04-3.18 (2H, m), 3.58-3.75 (8H, m), 4.34-4.51 (2H, m), 6.25-6.37 (1H, m), 7.09-7.20 (1H, m), 7.36-7.49 (2H, m), 7.49-7.89 (3H, m)
27	1	ESI+: 445
28	1	ESI+: 444 NMR1: 1.12-1.39 (4H, m), 1.79-2.00 (4H, m), 2.55-2.64 (1H, m), 3.5-3.77 (9H, m), 5.63 (1H, s), 6.88 (1H, d, J = 7.9 Hz), 7.35-7.47 (2H, m), 7.63-7.94 (2H, m), 8.35-8.39 (1H, m)
29	1	ESI+: 581 [M+Na]

[0582] [表 92]

[0583]

Ex	Syn	DATA
30	1	ESI+: 468 NMR1: 1.66-2.20 (2H, m), 2.49-3.04 (4H, m), 3.62-3.87 (8H, m), 4.21-4.35 (1H, m), 7.38-7.51 (3H, m), 7.63-8.11 (3H, m), 8.39-8.62 (1H, m), 11.60-11.69 (1H, m)
31	1	ESI+: 444
32	1	ESI+: 500 NMR1: 1.71-2.13 (2H, m), 2.50-2.95 (4H, m), 3.64-3.86 (8H, m), 4.28 (1H, br-s), 6.69 (2H, s), 7.38-7.51 (2H, m), 7.63-8.10 (3H, m), 8.39-8.61 (1H, m)
33	1	ESI+: 444 NMR1: 1.34-1.86 (8H, m), 2.81 (1H, br-s), 3.60-3.72 (8H, m), 3.80 (1H, br-s), 6.32 (1H, br-s), 6.73-6.99 (1H, m), 7.35-7.98 (5H, m)
34	1	ESI+: 580 [M+Na]
35	1	ESI+: 580 [M+Na]
36	1	ESI+: 567 [M+Na]
37	2	ESI+: 531 NMR1: 1.21-1.44 (4H, m), 1.80-2.00 (4H, m), 2.28 (2H, t, J = 5.2 Hz), 3.20-3.21 (3H, m), 3.51 (2H, m, J = 6.4 Hz), 3.46-3.57 (1H, m), 3.65-3.84 (9H, m), 7.40-7.51 (2H, m), 7.65-8.05 (4H, m), 8.42-8.58 (1H, m)
38	2	ESI+: 561 NMR1: 1.33-1.49 (4H, m), 1.75-2.02 (4H, m), 3.29-3.30 (3H, m), 3.47-3.51 (2H, m), 3.56-3.83 (12H, m), 3.86 (2H, s), 7.40-7.59 (3H, m), 7.65-8.05 (3H, m), 8.42-8.59 (1H, m)
39	2	ESI+: 533 NMR1: 1.26-1.52 (4H, m), 1.74-2.03 (4H, m), 3.41-3.88 (12H, m), 4.63-4.65 (1H, m), 5.42-5.46 (1H, m), 7.40-8.05 (6H, m), 8.42-8.59 (1H, m)
40	2	ESI+: 530 NMR1: 1.31-1.53 (4H, m), 1.73-2.05 (4H, m), 2.19-2.20 (6H, m), 2.83 (2H, s), 3.54-3.87 (10H, m), 7.40-7.65 (3H, m), 7.78-8.06 (3H, m), 8.42-8.59 (1H, m)

[0584] [表 93]

[0585]

Ex	Syn	DATA
41	2	ESI+: 544 NMR1: 1.30-1.47 (4H, m), 1.82-2.05 (4H, m), 2.84-2.85 (3H, m), 2.95-2.96 (3H, m), 3.55-3.85 (10H, m), 7.40-7.51 (2H, m), 7.65-8.05 (3H, m), 8.41-8.60 (2H, m)
42	2	ESI+: 557 NMR1: 1.20-1.44 (4H, m), 1.51-1.62 (4H, m), 1.79-1.87 (2H, m), 1.90-2.02 (2H, m), 2.25-2.35 (1H, m), 3.24-3.37 (2H, m), 3.47-3.57 (1H, m), 3.64-3.89 (11H, m), 7.40-7.51 (2H, m), 7.62-8.05 (4H, m), 8.41-8.58 (1H, m)
43	2	ESI+: 571 NMR1: 1.03-1.45 (8H, m), 1.57-2.10 (9H, m), 3.43-3.56 (1H, m), 3.63-3.86 (9H, m), 4.27-4.52 (1H, m), 7.42-8.05 (6H, m), 8.41-8.58 (1H, m)
44	2	ESI+: 585 NMR1: 0.99-1.43 (8H, m), 1.59-2.13 (9H, m), 3.19-3.22 (3H, m), 3.43-3.57 (1H, m), 3.63-3.88 (9H, m), 3.40-3.51 (2H, m), 7.58-8.05 (4H, m), 8.41-8.58 (1H, m)
45	2	ESI+: 585 NMR1: 1.17-1.84 (15H, m), 1.91-2.00 (2H, m), 2.12-2.22 (1H, m), 3.27-3.31 (2H, m), 3.42-3.58 (1H, m), 3.63-3.87 (9H, m), 4.36 (1H, t, J = 5.3 Hz), 7.40-7.62 (3H, m), 7.64-8.05 (3H, m), 8.41-8.58 (1H, m)
46	2	ESI+: 529 NMR1: 1.22-1.48 (4H, m), 1.75-1.85 (2H, m), 1.97-2.07 (2H, m), 2.19 (6H, s), 2.82 (2H, s), 3.55-3.87 (10H, m), 6.10 (1H, s), 7.37-7.54 (5H, m), 7.69-7.74 (1H, m), 7.83-7.87 (1H, m)
47	2	ESI+: 544 NMR1: 1.36-1.85 (6H, m), 1.91-2.08 (2H, m), 2.15-2.21 (6H, m), 2.65-3.10 (4H, m), 3.56-3.91 (10H, m), 7.39-7.58 (2H, m), 7.66-8.05 (3H, m), 8.42-8.58 (1H, m)

[0586] [表 94]

[0587]

Ex	Syn	DATA
48	2	ESI+: 543 NMR1: 1.27-1.70 (6H, m), 1.86-2.09 (2H, m), 2.17-2.18 (6H, m), 2.62-3.08 (4H, m), 3.58-4.25 (10H, m), 6.26-6.37 (1H, m), 6.92-7.06 (1H, m), 7.35-7.87 (5H, m)
49	2	ESI+: 529 NMR1: 1.24-1.47 (4H, m), 1.67-2.05 (4H, m), 2.18 (6H, s), 2.81 (2H, s), 3.49-3.77 (10H, m), 6.25-6.40 (1H, m), 6.88-7.09 (1H, m), 7.35-7.91 (6H, m)
50	2	ESI+: 577 [M+Na] NMR1: 1.15-1.47 (4H, m), 1.83-2.04 (4H, m), 3.15-3.28 (2H, m), 3.49-3.87 (10H, m), 6.24-6.37 (1H, m), 7.39-7.51 (2H, m), 7.65-8.01 (4H, m), 8.12-8.25 (1H, m) 8.39-8.60 (1H, m)
51	2	ESI+: 583
52	2	ESI+: 626
53	2	ESI+: 655
54	2	ESI+: 543
55	2	ESI+: 616 NMR1: 1.26-1.46 (6H, m), 1.35 (9H, s), 1.80-2.02 (4H, m), 2.80 (3H, s), 3.49-3.84 (10H, m), 7.39-7.51 (2H, m), 7.65-8.05 (4H, m), 8.41-8.59 (1H, m)
56	2	ESI+: 602 NMR1: 1.22-1.45 (5H, m), 1.39 (9H, s), 1.80-2.01 (4H, m), 3.42-3.84 (11H, m), 6.80-6.88 (1H, m), 7.40-8.05 (6H, m), 8.42-8.59 (1H, m)
57	2	ESI+: 663 [M+Na]
58	2	ESI+: 663 [M+Na]
59	2	ESI+: 573 [M+Na]
60	2	ESI+: 655
61	2	ESI+: 655
62	2	ESI+: 599 [M+Na]
63	2	ESI+: 605 [M+Na]
64	2	ESI+: 677 [M+Na]

[0588] [表 95]

[0589]

Ex	Syn	DATA
65	2	ESI+: 612 [M+Na]
66	2	ESI+: 598 [M+Na]
67	2	ESI+: 599 [M+Na]
68	2	ESI+: 569
69	2	ESI+: 652
70	2	ESI+: 641 [M+Na]
71	2	ESI+: 583
72	2	ESI+: 662 [M+Na]
73	2	ESI+: 677 [M+Na]
74	2	ESI+: 677 [M+Na]
75	2	ESI+: 655
76	2	ESI+: 677 [M+Na]
77	2	ESI+: 677 [M+Na]
78	2	ESI+: 610 [M+Na]
79	2	ESI+: 757 [M+Na]
80	2	ESI+: 663 [M+Na]
81	2	ESI+: 530
82	3	ESI+: 545 [M+Na] NMR1: 1.28-1.47 (4H, m), 1.90-2.03 (4H, m), 2.91-2.96 (3H, m), 3.07-3.19 (1H, m), 3.64-3.83 (9H, m), 7.00-7.08 (1H, m), 7.39-7.53 (2H, m), 7.63-8.07 (3H, m), 8.40-8.60 (1H, m)
83	3	ESI+: 591 NMR1: 1.31-1.47 (3H, m), 1.88-2.04 (3H, m), 3.15-3.36 (2H, m), 3.58-3.85 (9H, m), 4.37-4.47 (2H, m), 7.40-7.51 (2H, m), 7.62-8.05 (4H, m), 8.41-8.58 (1H, m)
84	3	ESI+: 549 NMR1: 0.85-0.98 (4H, m), 1.31-1.47 (4H, m), 1.90-2.06 (4H, m), 2.53-2.63 (1H, m), 3.04-3.21 (1H, m), 3.59-3.87 (9H, m), 7.03-7.12 (1H, m), 7.40-7.51 (2H, m), 7.65-8.05 (3H, m), 8.41-8.58 (1H, m)

[0590] [表 96]

[0591]

Ex	Syn	DATA
85	3	ESI+: 627 NMR1: 1.10-1.48 (5H, m), 1.81-2.08 (5H, m), 2.20-3.12 (4H, m), 3.62-3.86 (11H, m), 7.40-7.93 (6H, m), 8.40-8.60 (1H, m)
86	3	ESI+: 591 NMR1: 1.21-1.66 (10H, m), 1.79-1.99 (6H, m), 2.13-2.23 (1H, m), 2.96-3.15 (3H, m), 3.61-3.85 (9H, m), 6.99-7.03 (1H, m), 7..40-7.51 (2H, m), 7.64-8.05 (3H, m), 8.41-8.58 (1H, m)
87	3	ESI+: 585 NMR1: 1.15-1.35 (4H, m), 1.61-1.72 (2H, m), 1.80-1.91 (2H, m), 2.86-3.01 (1H, m), 3.56-3.83 (9H, m), 7.38-7.50 (2H, m), 7.57-8.03 (9H, m), 8.36-8.56 (1H, m)
88	3	ESI+: 599 NMR1: 1.23-1.41 (4H, m), 1.86-1.99 (4H, m), 2.95-3.09 (1H, m), 3.61-3.85 (9H, m), 4.33-4.34 (2H, m), 7.08-7.11 (1H, m), 7.34-7.50 (7H, m), 7.64-8.05 (3H, m), 8.41-8.58 (1H, m)
89	3	ESI+: 550 NMR1: 0.97 (3H, t, J = 7.4 Hz), 1.22-1.39 (4H, m), 1.59-1.72 (2H, m), 1.79-2.00 (4H, m), 2.91-3.11 (3H, m), 3.54-3.74 (9H, m), 6.26-6.39 (1H, m), 6.91-7.06 (2H, m), 7.36-7.88 (5H, m)
90	3	ESI+: 584 NMR1: 1.10-1.31 (4H, m), 1.53-1.93 (4H, m), 2.81-2.97 (1H, m), 3.51-3.73 (9H, m), 6.25-6.37 (1H, m), 6.83-6.96 (1H, m), 7.33-7.87 (11H, m)
91	3	ESI+: 598 NMR1: 1.13-1.36 (4H, m), 1.77-1.99 (4H, m), 2.87-3.06 (1H, m), 3.51-3.76 (9H, m), 4.31 (2H, s), 6.21-6.38 (1H, m), 6.89-7.08 (2H, m), 7.30-7.52 (8H, m), 7.73-7.88 (2H, m)
92	3	ESI+: 606 [M+Na]

[0592] [表 97]

[0593]

Ex	Syn	DATA
93	3	ESI+: 573 [M+Na] NMR1: 1.23-1.37 (4H, m), 1.84-2.01 (4H, m), 2.59-2.68 (6H, m), 2.88-3.04 (1H, m), 3.57-3.74 (9H, m), 6.25-6.38 (1H, m), 6.85-7.16 (4H, m), 7.36-7.58 (2H, m), 7.74-7.88 (2H, m)
94	3	ESI+: 598
95	3	ESI+: 606 [M+Na]
96	3	ESI+: 609
97	3	ESI+: 606
98	3	ESI+: 584 [M+Na]
99	4	ESI+: 472 NMR1: 1.13-1.37 (4H, m), 1.75-2.11 (4H, m), 2.18 (6H, s), 3.60-3.84 (9H, m), 6.09 (1H, s), 7.36-7.66 (4H, m), 7.69-7.74 (1H, m), 7.83-7.34 (1H, m)
100	4	ESI+: 473 NMR1: 1.00 (3H, t, J = 7.0 Hz), 0.92-1.39 (4H, m), 1.78-2.01 (4H, m), 2.32-2.53 (2H, m), 2.56 (2H, q, J = 7.0 Hz), 3.55-3.85 (9H, m), 7.40-7.51 (2H, m), 7.64-8.05 (3H, m), 8.42-8.58 (1H, m)
101	4	ESI+: 535 NMR1: 1.09-1.36 (4H, m), 1.88-2.03 (5H, m), 2.29-2.42 (1H, m), 3.62-3.83 (11H, m), 7.19-7.51 (7H, m), 7.64-8.05 (3H, m), 8.42-8.57 (1H, m)
102	4	ESI+: 551 NMR1: 1.28-1.60 (4H, m), 1.99-2.26 (4H, m), 2.94-3.07 (1H, m), 3.62-3.85 (9H, m), 4.01-4.08 (2H, m), 6.82 (2H, d), 7.34-7.53 (4H, m), 7.65-8.05 (3H, m), 8.42-8.57 (1H, m), 8.90 (1H, br-s), 9.70 (1H, s)
103	4	ESI+: 551 NMR1: 1.29-1.63 (4H, m), 1.99-2.27 (4H, m), 2.97-3.11 (1H, m), 3.66-3.85 (9H, m), 4.04-4.13 (2H, m), 6.81-6.98 (3H, m), 7.22-7.54 (3H, m), 7.65-8.05 (3H, m), 8.42-8.58 (1H, m), 8.93-9.11 (1H, m), 9.69 (1H, s)
104	4	ESI+: 551 NMR1: 1.15-1.32 (4H, m), 1.89-2.04 (4H, m), 2.31-2.55 (3H, m), 3.62-3.83 (9H, m), 3.89 (2H, s), 6.66-6.72 (2H, m), 7.04-7.08 (2H, m), 7.40-7.50 (2H, m), 7.64-8.05 (3H, m), 8.41-8.57 (1H, m)

[0594] [表 98]

[0595]

Ex	Syn	DATA
105	4	ESI+: 595 NMR1: 1.10-1.36 (4H, m), 1.89-2.01 (4H, m), 2.29-2.42 (1H, m), 3.65-3.83 (14H, m), 3.97 (2H, t, J = 4.9 Hz), 4.82-4.88 (1H, m), 6.77-6.93 (3H, m), 7.18-7.51 (3H, m), 7.64-8.04 (3H, m), 8.41-8.57 (1H, m)
106	4	ESI+: 636 NMR1: 1.02-1.56 (7H, m), 1.76-2.01 (4H, m), 2.24-2.37 (1H, m), 3.01-3.10 (2H, m), 3.63-3.85 (9H, m), 5.01 (2H, s), 7.22-7.51 (8H, m), 7.64-8.05 (4H, m), 8.41-8.58 (1H, m)
107	4	ESI+: 555 NMR1: 0.73-1.39 (11H, m), 0.91 (3H, t, J = 6.4 Hz), 1.56-1.99 (9H, m), 2.33-2.57 (2H, m), 3.64-3.85 (8H, m), 7.40-7.51 (2H, m), 7.64-8.05 (3H, m), 8.41-8.58 (1H, m), 8.62 (1H, br-s)
108	4	ESI+: 565 NMR1: 1.13-1.37 (8H, m), 1.78-2.38 (6H, m), 3.62-4.17 (10H, m), 6.64-6.74 (2H, m), 7.03-7.07 (2H, m), 7.39-7.50 (2H, m), 7.64-8.03 (3H, m), 8.41-8.56 (1H, m)
109	4	ESI+: 618 NMR1: 1.30-1.58 (4H, m), 1.98-2.28 (7H, m), 2.87-2.47 (7H, m), 3.63-3.83 (9H, m), 4.20-4.29 (2H, m), 7.38-7.66 (7H, m), 7.77-8.05 (2H, m), 8.41-8.57 (1H, m), 9.09-9.28 (1H, m), 10.94 (1H, br-s)
110	4	ESI+: 625 NMR1: 1.10-1.26 (2H, m), 1.48-1.61 (2H, m), 1.83-2.05 (4H, m), 2.37-2.58 (1H, m), 3.54-3.84 (13H, m), 7.19-7.49 (12H, m), 7.64-8.02 (3H, m), 8.40-8.54 (1H, m)
111	4	ESI+: 501 NMR1: 0.96 (6H, t, J = 7.1 Hz), 1.22-1.40 (4H, m), 1.68-2.05 (4H, m), 2.43-2.49 (4H, m), 3.65-3.82 (9H, m), 7.40-7.51 (2H, m), 7.78-8.05 (3H, m), 8.42-8.58 (1H, m)
112	4	ESI+: 569
113	4	ESI+: 569
114	4	ESI+: 569

[0596] [表 99]

[0597]

Ex	Syn	DATA
115	5	ESI+ 538 [M+Na] NMR1: 1.37-1.62 (6H, m), 1.96-2.04 (2H, m), 2.56-2.65 (6H, m), 3.70-3.98 (9H, m), 6.15 (1H, m), 7.42-7.51 (2H, m), 7.65-8.05 (3H, m), 8.42-8.58 (1H, m)
116	5	ESI+: 618 [M+Na] NMR1: 1.18-1.29 (2H, m), 1.33-1.44 (2H, m), 1.87-2.00 (4H, m), 3.70-3.78 (9H, m), 4.17-4.12 (2H, m), 5.80-5.94 (1H, m), 6.17-6.28 (1H, m), 7.11-7.16 (2H, m), 7.25-7.30 (2H, m), 7.40-7.51 (2H, m), 7.65-8.05 (3H, m), 8.41-8.58 (1H, m)
117	5	ESI+: 604 [M+Na] NMR1: 1.22-1.48 (4H, m), 1.91-2.03 (4H, m), 3.41-3.52 (1H, m), 3.67-3.85 (9H, m), 6.07 (1H, dd, J = 8.4, 4.2 Hz), 7.02-7.13 (2H, m), 7.36-7.52 (4H, m), 7.66-7.06 (3H, m), 8.23-8.78 (2H, m)
118	5	ESI+: 617 [M+Na] NMR1: 1.17-1.38 (4H, m), 1.78-2.01 (4H, m), 3.59-3.72 (9H, m), 4.17 (2H, br-s), 5.82 (1H, br-s), 6.13-6.37 (2H, m), 6.89-7.05 (1H, m), 7.09-7.12 (2H, m), 7.23-7.30 (2H, m), 7.37-7.52 (2H, m), 7.75-7.88 (2H, m)
119	5	ESI+: 632[M+Na] NMR1: 1.36-1.52 (2H, m), 1.52-1.66 (4H, m), 1.96-2.05 (2H, m), 2.71 (3H, S), 3.66-3.84 (8H, m), 3.92-4.07 (2H, m), 4.22 (2H, d, J = 6 Hz), 6.84-6.90 (1H, m), 7.09-7.15 (2H, m), 7.26-7.31 (2H, m), 7.40-7.54 (2H, m), 7.66-8.05 (3H, m), 8.42-8.58 (1H, m)
120	5	ESI+: 581 NMR1: 1.02-1.42 (4H, m), 169-2.03 (4H, m), 3.60-3.74 (8H, m), 6.01-6.07 (1H, m), 6.26-6.38 (1H, m), 6.92-7.08 (2H, m), 7.33-7.88 (6H, m), 8.28-8.43 (1H, m)
121	5	ESI+: 607 NMR1: 1.08-1.39 (4H, m), 1.79-2.01 (4H, m), 3.59-3.74 (12H, m), 4.08-4.11 (2H, m), 5.71-5.79 (1H, m), 6.01-6.16 (1H, m), 6.25-6.37 (1H, m), 6.84-7.04 (3H, m), 7.05-7.19 (2H, m), 7.37-7.55 (2H, m), 7.75-7.96 (2H, m)

[0598] [表 100]

[0599]

Ex	Syn	DATA
122	5	ESI+: 669 [M+Na] NMR1: 1.16-1.42 (4H, m), 1.84-2.06 (4H, m), 3.36-3.48 (1H, m), 3.59-3.75 (9H, m), 6.10-6.14 (1H, m), 6.28-6.38 (1H, m), 6.93-7.06 (1H, m), 7.18-7.31 (2H, m), 7.38-7.87 (8H, m), 8.46-8.62 (1H, m)
123	5	ESI+: 610 [M+Na] NMR1: 1.19-1.44 (4H, m), 1.86-2.05 (4H, m), 3.36-3.51 (1H, m), 3.58-3.75 (9H, m), 6.26-6.38 (1H, m), 6.91-7.97 (1H, m), 7.38-7.87 (8H, m), 8.86-8.96 (1H, m)
124	5	ESI+: 599 [M+Na] NMR1: 1.12-1.38 (4H, m), 1.79-2.02 (4H, m), 3.60-3.74 (9H, m), 4.19 (2H, d, J = 6 Hz), 5.77-5.87 (1H, m), 6.10-6.38 (2H, m), 6.90-7.05 (1H, m), 7.18-7.36 (5H, m), 7.36-7.59 (2H, m), 7.63-7.88 (2H, m)
125	5	ESI+: 610 [M+Na]
126	5	ESI+: 610 [M+Na]
127	5	ESI+: 624 [M+Na]
128	5	ESI+: 585 [M+Na]
129	5	ESI+: 619 [M+Na]
130	5	ESI+: 628 [M+Na]
131	5	ESI+: 624 [M+Na]
132	5	ESI+: 585 [M+Na]
133	5	ESI+: 619 [M+Na]
134	5	ESI+: 619 [M+Na]
135	5	ESI+: 619 [M+Na]
136	6	ESI+: 580 [M+Na] NMR1: 1.63-2.50 (2H, m), 3.35-3.79 (2H, m), 1.82-2.00 (4H, m), 3.51-3.82 (16H, m), 5.52-5.74 (1H, m), 7.41-7.50 (2H, m), 7.65-8.05 (3H, m), 8.41-8.59 (1H, m)
137	6	ESI+: 573 NMR1: 1.30-1.42 (4H, m), 1.81-1.87 (2H, m), 1.91-1.99 (2H, m), 2.16 (6H, s), 2.28-2.23 (2H, m), 2.77 (3H, s), 3.22-3.46 (3H, m), 3.67-3.81 (9H, m), 6.14-6.33 (1H, m), 7.40-7.51 (2H, m), 7.64-8.05 (3H, m), 8.42-8.58 (1H, m)

[0600] [表 101]

[0601]

Ex	Syn	DATA
138	6	ESI+: 568 [M+Na] NMR1: 1.17-1.47 (4H, m), 1.84-1.91 (4H, m), 3.11-3.17 (1H, m), 3.67-3.83 (11H, m), 5.50-5.94 (2H, m), 7.41-7.50 (2H, m), 7.66-8.04 (3H, m), 8.41-8.59 (1H, m)
139	6	ESI+: 600 NMR1: 1.06-1.38 (4H, m), 1.77-2.02 (4H, m), 2.26-3.14 (4H, m), 3.55-3.74 (10H, m), 5.50-5.65 (1H, m), 6.27-6.37 (1H, m), 6.90-7.09 (1H, m), 7.37-7.96 (6H, m)
140	6	ESI+: 599 NMR1: 1.00-2.20 (15H, m), 2.89-3.14 (1H, m), 2.29-2.37 (6H, m), 3.08-3.12 (2H, m), 3.57-3.84 (9H, m), 5.48-5.65 (1H, m), 6.25-6.37 (1H, m), 6.88-7.05 (1H, m), 7.35-8.01 (5H, m)
141	6	ESI+: 614
142	6	ESI+: 645 NMR1: 1.09-1.34 (4H, m), 1.79-2.02 (4H, m), 3.56-3.81 (10H, m), 4.27 (2H, d, J = 6 Hz), 5.87-5.95 (1H, m), 6.24-6.41 (2H, m), 6.87-7.04 (1H, m), 7.37-7.60 (4H, m), 7.63-7.72 (2H, m), 7.75-7.91 (2H, m)
143	6	ESI+: 600 [M+Na] NMR1: 1.12-1.40 (4H, m), 1.81-2.01 (4H, m), 3.59-3.76 (9H, m), 4.21 (2H, d, J = 6 Hz), 5.91-5.99 (1H, m), 6.23-6.41 (2H, m), 6.87-7.04 (1H, m), 7.19-7.24 (2H, m), 7.37-7.61 (2H, m), 7.64-7.90 (2H, m), 8.31-8.50 (1H, m)
144	6	ESI+: 624 [M+Na]
145	6	ESI+: 577 [M+Na]
146	6	ESI+: 562 [M+Na]
147	6	ESI+: 611
148	7	ESI+: 544
149	8	ESI+: 459
150	8	ESI+: 458 NMR1: 0.82-1.03 (4H, m), 1.35-2.60 (2H, m), 1.65-1.82 (4H, m), 2.99-3.03 (2H, m), 3.56-3.75 (8H, m), 6.23-6.37 (1H, m), 7.09-7.17 (1H, m), 7.37-7.48 (2H, m), 7.75-7.79 (1H, m), 7.82-7.88 (1H, m)

[0602] [表 102]

[0603]

Ex	Syn	DATA
151	8	ESI+: 516 NMR1: 1.28-1.45 (4H, m), 1.77-2.03 (4H, m), 2.23 (3H, s), 2.99 (2H, s), 3.52-3.84 (10H, m), 7.40-8.05 (6H, m), 8.41-8.60 (1H, m)
152	8	ESI+: 529
153	8	ESI+: 541
154	8	ESI+: 541
155	8	ESI+: 458
156	8	ESI+: 555
157	8	ESI+: 555
158	8	ESI+: 555
159	8	ESI+: 555
160	8	ESI+: 555
161	8	ESI+: 555
162	8	ESI+: 555
163	8	ESI+: 541
164	8	ESI+: 570
165	8	ESI+: 445 NMR1: 1.13-1.28 (2H, m), 1.41-1.73 (3H, m), 1.78-1.87 (2H, m), 2.05-2.15 (2H, m), 2.57-2.69 (1H, m), 3.66-3.76 (8H, m), 4.97-5.07 (1H, m), 6.38 (1H, s), 7.39-7.49 (2H, m), 7.52 (1H, t), 7.72-7.77 (1H, m), 7.84-7.88 (1H, m)
166	8	ESI+: 459 NMR1: 0.98-1.15 (4H, m), 1.62-1.86 (5H, m), 3.64-3.78 (8H, m), 4.20 (2H, d), 6.43 (1H, s), 7.39-7.50 (2H, m), 7.54 (1H, t), 7.74-7.79 (1H, m), 7.84-7.89 (1H, m)
167	8	ESI+: 476
168	8	ESI+: 476
169	8	ESI+: 445
170	9	ESI+: 564, 566
171	9	ESI+: 586 [M+Na]

[0604] [表 103]

[0605]

Ex	Syn	DATA
172	10	ESI+: 514 NMR1: 1.19-1.36 (4H, m), 1.79-2.22 (4H, m), 3.41-3.50 (2H, m), 3.43-3.80 (16H, m), 6.24-6.37 (1H, m), 6.89-7.03 (1H, m), 7.37-7.55 (2H, m), 7.64-6.96 (3H, m)
173	10	ESI+: 514 NMR1: 1.39-1.89 (8H, m), 2.09-2.18 (1H, m), 2.38-2.47 (4H, m), 3.51-3.77 (12H, m), 3.91 (1H, br-s), 6.32 (1H, br-s), 6.98 (1H, br-s), 7.34-8.04 (5H, m)
174	10	ESI+: 528 NMR1: 0.75-1.58 (8H, m), 1.75-1.88 (4H, m), 2.06-1.20 (1H, m), 2.99-3.20 (1H, m), 3.46-3.74 (9H, m), 6.18-6.40 (1H, m), 7.09-7.18 (1H, m), 7.38-7.50 (2H, m), 7.50-7.89 (3H, m)
175	10	ESI+: 512
176	10	ESI+: 498
177	10	ESI+: 526
178	10	ESI+: 512
179	10	ESI+: 554
180	10	ESI+: 526
181	11	ESI+: 549 [M+Na] NMR1: 1.34-1.50 (2H, m), 1.51-1.75 (8H, m), 1.96-2.07 (2H, m), 2.18-2.26 (2H, m), 3.15-3.22 (2H, m), 3.64-3.86 (9H, m), 4.24-4.36 (1H, m), 7.38-7.55 (2H, m), 7.64-8.06 (3H, m), 8.40-8.60 (1H, m)
182	11	ESI+: 535 [M+Na]
183	11	ESI+: 512 NMR1: 1.32-1.43 (2H, m), 1.52-1.69 (2H, m), 1.75-2.03 (6H, m), 2.15-2.25 (2H, m), 3.59-3.88 (9H, m), 4.03-4.13 (1H, m), 6.35 (1H, br-s), 7.07-7.15 (1H, m), 7.35-7.98 (5H, m)
184	11	ESI+: 548 [M+Na]
185	11	ESI+: 534 [M+Na]

[0606] [表 104]

[0607]

Ex	Syn	DATA
186	12	ESI+: 570 NMR1: 1.32-1.57 (10H, m), 1.74-2.01 (4H, m), 2.29-2.40 (4H, m), 2.82-2.83 (2H, m), 3.53-3.84 (10H, m), 7.39-7.52 (3H, m), 7.64-8.05 (3H, m), 8.41-8.58 (1H, m)
187	12	ESI+: 555
188	12	ESI+: 619
189	12	ESI+: 555
190	12	ESI+: 583
191	12	ESI+: 670
192	12	ESI+: 541
193	14	ESI+: 509 [M+Na] NMR1: 1.20-1.45 (4H, m), 1.76-2.02 (7H, m), 3.46-3.56 (1H, m), 3.65-3.85 (9H, m), 7.49-7.54 (2H, m), 7.63-8.07 (4H, m), 8.40-8.61 (1H, m)
194	14	ESI+: 508 [M+Na]
195	14	ESI+: 508 [M+Na] NMR1: 1.19-1.38 (4H, m), 1.78 (3H, s), 1.79-2.08 (4H, m), 3.53 (1H, br-s), 3.66 (8H, br-s), 3.80 (1H, br-s), 6.10 (1H, s), 7.37-7.66 (4H, m), 7.68-7.75 (2H, m), 7.84 (1H, d, J = 7.6 Hz)
196	14	ESI+: 500 NMR1: 1.33-1.70 (5H, m), 1.89-2.06 (5H, m), 2.47-2.50 (3H, m), 2.64-2.84 (2H, m), 3.58-3.74 (9H, m), 6.25 (1H, s), 6.63 (1H, d, J = 7.5 Hz), 7.36-7.66 (3H, m), 7.72 (1H, d, J = 7.8 Hz), 7.82 (1H, d, J = 7.6 Hz)
197	15	ESI+: 458 NMR1: 0.94-1.33 (3H, m), 1.04 (3H, d, J = 6 Hz), 1.71-2.34 (7H, m), 3.59-3.71 (9H, m), 6.24-6.38 (1H, m), 6.85-7.01 (1H, m), 7.76-7.86 (2H, m)
198	15	ESI+: 472 NMR1: 1.14-1.32 (4H, m), 1.71-2.26 (11H, m), 3.56-3.73 (9H, m), 6.22-6.37 (1H, m), 6.84-7.04 (1H, m), 7.33-7.97 (4H, m)

[0608] [表 105]

[0609]

Ex	Syn	DATA
199	15	ESI+: 486 NMR1: 0.81-1.01 (2H, m), 1.04-1.27 (2H, m), 1.39-1.53 (1H, m), 1.73-1.88 (4H, m), 2.01-2.10 (1H, m), 2.10-2.38 (4H, m), 3.03-3.18 (2H, m), 3.58-3.73 (8H, m), 6.24-6.38 (1H, m), 7.10-7.18 (1H, m), 7.37-7.47 (2H, m), 7.50-7.88 (2H, m)
200	15	ESI+: 472 NMR1: 0.82-1.01 (4H, m), 1.38-1.61 (2H, m), 1.68-1.92 (4H, m), 2.12-2.26 (3H, m), 3.03-3.18 (2H, m), 3.58-3.73 (8H, m), 6.25-6.37 (1H, m), 7.10-7.17 (1H, m), 7.37-7.48 (2H, m), 7.49-7.89 (3H, m)
201	16	ESI+: 528 NMR1: 0.89-1.13 (2H, m), 1.37-1.60 (3H, m), 1.80-2.00 (6H, m), 2.10-2.24 (2H, m), 2.96-3.14 (2H, m), 3.30-3.41 (2H, m), 3.45-3.78 (9H, m), 3.84-3.98 (4H, m), 6.36-6.47 (1H, m), 7.30-7.71 (4H, m), 7.71-8.00 (3H, m), 11.04-11.32 (1H, m)
202	16	ESI+: 526
203	16	ESI+: 526
204	16	ESI+: 569
205	21	ESI+: 569
206	16	ESI+: 518 NMR1: 0.93-1.11 (2H, m), 1.35-1.62 (3H, m), 1.83-2.13 (5H, m), 2.66-2.78 (3H, m), 3.06-3.27 (2H, m), 3.30-3.74 (10H, m), 4.71-5.02 (2H, m), 6.28-6.43 (1H, m), 7.18-7.33 (1H, m), 7.38-7.50 (2H, m), 7.50-7.88 (3H, m), 10.21-10.46 (1H, m)
207	16	ESI+: 530
208	17	ESI+: 543
209	18	ESI+: 585 [M+Na] NMR1: 1.11-1.28 (2H, m), 1.42-1.60 (2H, m), 1.67-1.94 (5H, m), 2.14-2.26 (2H, m), 3.14 (2H, t), 3.22 (2H, t), 3.61-3.81 (8H, m), 4.21 (2H, d), 6.44 (1H, s), 7.38-7.50 (2H, m), 7.54 (1H, t), 7.77 (1H, d), 7.87 (1H, d)
210	20	ESI+: 651 [M+Na]
211	21	ESI+: 569
212	22	ESI+: 567 [M+Na]

[0610] [表 106]

[0611]

Ex	Syn	DATA
213	22	ESI+: 581 [M+Na]
214	22	ESI+: 598 [M+Na]
215	22	ESI+: 598 [M+Na]
216	23	ESI+: 529 NMR1: 1.10-1.26 (2H, m), 1.42-1.56 (2H, m), 1.71-1.84 (1H, m), 1.93-2.03 (2H, m), 2.13-2.22 (2H, m), 3.03-3.83 (15H, m), 3.94-4.01 (2H, m), 4.24 (2H, d), 6.43 (1H, s), 7.39-7.50 (2H, m), 7.54 (1H, t), 7.74-7.78 (1H, m), 7.85-7.89 (1H, m), 10.32 (1H, br-s)
217	23	ESI+: 546
218	23	ESI+: 546
219	26	ESI+: 530 NMR1: 0.82-1.01 (2H, m), 1.08-1.23 (2H, m), 1.37-1.52 (1H, m), 1.66-1.86 (4H, m), 1.96 (3H, s), 2.16 (3H, s), 2.23-2.34 (1H, m), 3.01-3.16 (2H, m), 3.19-3.24 (4H, m), 3.58-3.73 (8H, m), 6.25-6.37 (1H, m), 7.08-7.18 (1H, m), 7.37-7.48 (2H, m), 7.50-7.88 (3H, m)

[0612] [表 107]

[0613]

Ex	Syn	DATA
220	2	ESI+: 543
221	4	ESI+: 486
222	8	ESI+: 458
223	23	ESI+: 528
224	2	ESI+: 724 [M+Na]
225	225	ESI+: 601
226	10	ESI+: 516
227	10	ESI+: 574
228	25	ESI+: 562
229	25	ESI+: 598 [M+Na] NMR1: 0.99-1.14 (2H, m), 1.44-1.61 (3H, m), 1.87-1.98 (2H, m), 2.12-2.22 (2H, m), 2.99-4.56 (19H, m), 6.15 (1H, s), 7.37-7.68 (4H, m), 7.70-7.75 (1H, m), 7.83-7.88 (1H, m)
230	258	ESI+: 584 [M+Na]
231	258	ESI+: 598 [M+Na] NMR1: 0.81-1.04 (2H, m), 1.12-1.31 (2H, m), 0.81-1.31 (1H, m), 1.39-1.52 (1H, m), 1.66-1.88 (4H, m), 2.85-3.04 (8H, m), 3.04-3.18 (2H, m), 3.57-3.73 (8H, m), 6.25-6.37 (1H, m), 7.11-7.19 (1H, t, J = 5.6 Hz), 7.35-7.88 (5H, m)
232	258	ESI+: 598 [M+Na]
233	2	ESI+: 691 [M+Na]
234	2	ESI+: 662 [M+Na]
235	2	ESI+: 691 [M+Na]
236	2	ESI+: 662 [M+Na]
237	10	ESI+: 626
238	10	ESI+: 573
239	239	ESI+: 605
240	18	ESI+: 584 [M+Na]
241	18	ESI+: 584 [M+Na]
242	3	ESI+: 634 [M+Na]
243	4	ESI+: 542

[0614] [表 108]

[0615]

Ex	Syn	DATA
244	4	ESI+: 558
245	245	ESI+: 574
246	275,16	ESI+: 556 NMR1: 0.79-1.29 (8H, m), 1.42-1.65 (3H, m), 1.80-1.94 (2H, m), 2.01-2.19 (2H, m), 2.7 5-2.87 (1H, m), 3.06-3.22 (2H, m), 3.39-3.85 (14H, m), 6.27-6.41 (1H, m), 7.17-7.28 (1H, m), 7.37-7.89 (5H, m), 8.94-9.14 (1H, m)
247	10	ESI+: 592
248	10	ESI+: 726
249	10	ESI+: 542
250	26,16	ESI+: 578
251	26	ESI+: 698
252	26,16	ESI+: 578
253	26	ESI+: 698
254	26	ESI+: 578
255	26	ESI+: 698
256	4	ESI+: 564
257	18	ESI+: 584 [M+Na]
258	258	ESI+: 612 [M+Na]
259	26,16	ESI+: 548
260	26	ESI+: 638
261	26,16	ESI+: 592
262	26,16	ESI+: 587
263	4,16	ESI+: 556
264	26,16	ESI+: 563
265	26,16	ESI+: 576
266	26,16	ESI+: 570
267	26,16	ESI+: 596
268	26,16	ESI+: 594
269	26,16	ESI+: 533 [M+Na]
270	26,16	ESI+: 555

[0616] [表 109]

[0617]

Ex	Syn	DATA
271	26,16	ESI+: 570 NMR1: 0.28-0.42 (2H, m), 0.58-0.68 (2H, m), 0.92-1.26 (4H, m), 1.36-1.64 (3H, m), 1.80-2.06 (5H, m), 2.97-3.22 (4H, m), 3.04-3.18 (2H, m), 3.53-3.77 (10H, m), 2.27-6.41 (1H, m), 7.15-7.26 (1H, m), 7.35-7.88 (5H, m), 8.93-8.09 (1H, m)
272	279,16	ESI+: 536
273	26,16	ESI+: 593
274	386,16	ESI+: 516 NMR1: 0.78-1.01 (3H, m), 1.07-1.31 (3H, m), 1.39-1.55 (1H, m), 1.66-1.88 (4H, m), 2.12-1.19 (3H, br s), 2.22-2.34 (1H, m), 3.03-3.18 (2H, m), 3.35-3.44 (1H, m), 3.59-3.78 (8H, m), 4.20 (1H, t, J = 4.8 Hz), 6.25-6.37 (1H, m), 7.09-7.17 (1H, m), 7.38-7.91 (5H, m)
275	275	ESI+: 556
276	14	ESI+: 509 [M+Na]
277	3	ESI+: 545 [M+Na]
278	1,16	ESI+: 541
279	279	ESI+: 536
280	26,16	ESI+: 544 NMR1: 0.82-1.12 (2H, m), 1.12-1.29 (1H, m), 1.33-1.61 (3H, m), 1.82-2.04 (6H, m), 2.66 (3H, s), 2.93-3.05 (1H, m), 3.05-3.24 (3H, m), 3.24 (3H, s), 3.35-3.42 (2H, m), 3.59-3.75 (8H, m), 6.28-6.42 (1H, m), 7.17-7.25 (1H, m), 7.38-7.90 (5H, m), 9.46-9.65 (1H, m)
281	26	ESI+: 504
282	26,16	ESI+: 550
283	26,16	ESI+: 532
284	279,16	ESI+: 554
285	26,16	ESI+: 530
286	2	ESI+: 589
287	275,16	ESI+: 544
288	1	ESI+: 586
289	289	ESI+: 486

[0618] [表 110]

[0619]

Ex	Syn	DATA
290	333,16	ESI+: 578 [M+Na]
291	1	ESI+: 559
292	23	ESI+: 556
293	8	ESI+: 459
294	23	ESI+: 529
295	295	ESI+: 627
296	295	ESI+: 627
297	8	ESI+: 527
298	8	ESI+: 527
299	4	ESI+: 486
300	26	ESI+: 500
301	26	ESI+: 500
302	4,16	ESI+: 541
303	4,16	ESI+: 541
304	26,16	ESI+: 532
305	26,16	ESI+: 546
306	26,16	ESI+: 558
307	295,16	ESI+: 528
308	295,16	ESI+: 544
309	295,16	ESI+: 544
310	295,16	ESI+: 562
311	295,16	ESI+: 562
312	295,16	ESI+: 544
313	295,16	ESI+: 544
314	295,16	ESI+: 530
315	295,16	ESI+: 530
316	295,16	ESI+: 530
317	295,16	ESI+: 530
318	295,16	ESI+: 548
319	295,16	ESI+: 548
320	335	ESI+: 550 [M+Na]

[0620] [表 111]

[0621]

Ex	Syn	DATA
321	295,16	ESI+: 562
322	295,16	ESI+: 562
323	4,16	ESI+: 522
324	4	ESI+: 536
325	325	ESI+: 518
326	326	ESI+: 562
327	4	ESI+: 518
328	328	ESI+: 564 [M+Na]
329	325	ESI+: 504
330	15	ESI+: 532 NMR1: 0.77-1.04 (3H, m), 1.07-1.31 (6H, m), 1.37-1.54 (1H, m), 1.65-1.87 (4H, m), 2.21 (3H, s), 2.25-2.35 (1H, m), 3.01-3.17 (2H, m), 3.56-3.75 (8H, m), 4.57-4.80 (1H, m), 6.25-6.38 (1H, m), 7.10-7.19 (1H, m), 7.37-7.89 (5H, m)
331	15	ESI+: 532
332	15	ESI+: 550
333	333	ESI+: 578
334	326,16	ESI+: 546
335	335	ESI+: 542
336	326	ESI+: 562
337	326	ESI+: 579 [M+Na]
338	4	ESI+: 560 NMR1: 0.73-1.05 (8H, m), 1.08-1.35 (4H, m), 1.38-1.51 (1H, m), 1.51-1.62 (1H, m), 2.36-2.50 (3H, m), 3.00-3.18 (3H, m), 3.56-3.76 (8H, m), 4.03-4.34 (2H, m), 6.24-6.40 (1H, m), 7.07-7.19 (1H, m), 7.37-7.90 (5H, m)
339	4,16	ESI+: 560
340	26,16	ESI+: 514
341	326	NMR1: 0.78-0.86 (3H, m), 0.86-1.01 (2H, m), 1.09-1.23 (4H, m), 1.26 (2H, d, J = 6.4 Hz), 1.29-1.39 (2H, m), 1.40-1.53 (1H, m), 1.65-1.86 (4H, m), 2.35-2.45 (3H, m), 3.04-3.19 (1H, m), 3.6-3.74 (8H, m), 4.49-4.70 (1H, m), 6.26-6.37 (1H, m), 7.05-7.14 (1H, m), 7.37-7.48 (5H, m)

[0622] [表 112]

[0623]

Ex	Syn	DATA
342	343,16	ESI+: 548
343	343	FAB+: 534
344	4,16	ESI+: 546 NMR1: 0.98-0.38 (8H, m), 1.43-1.65 (3H, m), 1.79-1.94 (2H, m), 1.95-2.17 (4H, m), 3.05-3.39 (5H, m), 3.59-3.72 (8H, m), 3.82-3.98 (1H, m), 4.59-4.93 (2H, m), 6.25-6.43 (1H, m), 7.17-7.29 (1H, m), 7.37-7.88 (5H, m), 9.33-9.61 (1H, m)
345	345	ESI+: 560
346	26	ESI+: 558
347	26	ESI+: 630
348	343	ESI+: 516
349	343	ESI+: 530
350	343	ESI+: 546
351	343	ESI+: 634
352	353	ESI+: 572
353	353	ESI+: 556
354	343	ESI+: 532
355	353	ESI+: 556
356	343	ESI+: 546
357	2	ESI+: 516
358	353	ESI+: 542
359	2	ESI+: 529
360	2	ESI+: 557
361	353	ESI+: 542
362	26,16	ESI+: 558
363	4	ESI+: 544 NMR1: 0.81-1.01 (5H, m), 1.07-1.28 (2H, m), 1.37-1.56 (1H, m), 1.65-1.86 (4H, m), 2.34-2.44 (1H, m), 3.02-3.17 (2H, m), 3.21 (3H, s), 3.25-3.31 (3H, m), 3.50-3.75 (8H, m), 4.47-4.70 (1H, m), 6.25-6.37 (1H, m), 7.01-7.16 (1H, m), 7.37-7.88 (5H, m)
364	1	ESI+: 572

[0624] [表 113]

[0625]

Ex	Syn	DATA
365	1	ESI+: 572
366	1	ESI+: 586
367	289	ESI+: 472
368	289	ESI+: 472
369	289	ESI+: 486
370	23	ESI+: 542 NMR1: 0.93-1.10 (2H, m), 1.25 (3H, d, J = 6.7 Hz), 1.39-1.59 (3H, m), 1.86-1.94 (2H, m), 2.13-2.21 (2H, m), 2.98-3.27 (5H, m), 3.32-3.39 (2H, m), 3.43-3.76 (4H, m), 3.86-3.97 (5H, m), 4.07-4.15 (1H, m), 4.38-4.48 (1H, m), 6.36 (1H, s), 7.40-7.72 (4H, m), 7.77 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 8.0 Hz)
371	23	ESI+: 542 NMR1: 0.93-1.07 (2H, m), 1.25 (3H, d, J = 6.8 Hz), 1.39-1.59 (3H, m), 1.86-1.94 (2H, m), 2.12-2.21 (2H, m), 2.98-3.28 (5H, m), 3.31-3.39 (2H, m), 3.43-3.65 (3H, m), 3.71-3.77 (1H, m), 3.87-3.97 (5H, m), 4.07-4.16 (1H, m), 4.38-4.49 (1H, m), 6.38 (1H, s), 7.40-7.69 (4H, m), 7.77 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 8.0 Hz)
372	23	ESI+: 556
373	343	ESI+: 560
374	326	ESI+: 576 NMR1: 7.94-1.03 (2H, m), 1.08-1.30 (5H, m), 1.38-1.53 (1H, m), 1.64-1.87 (4H, m), 2.54-2.66 (3H, m), 3.02-3.16 (2H, m), 3.21 (3H, s), 3.29 (3H, s), 3.59-3.76 (8H, m), 4.47-4.70 (1H, m), 6.25-6.37 (1H, m), 7.08-7.18 (1H, m), 7.37-7.89 (5H, m)
375	15	ESI+: 544 NMR1: 0.80-0.98 (2H, m), 1.03 (6H, s), 1.10-1.31 (2H, m), 1.39-1.62 (1H, m), 1.67-1.87 (4H, m), 2.20-2.33 (6H, m), 3.01-3.19 (2H, m), 3.58-3.75 (8H, m), 3.89 (1H, s), 6.25-6.37 (1H, m), 7.07-7.15 (1H, m), 7.38-7.87 (5H, m)
376	22	ESI+: 586
377	8	ESI+: 486
378	23	ESI+: 556

[0626] [表 114]

[0627]

Ex	Syn	DATA
379	26	ESI+: 530
380	26	ESI+: 530
381	417	ESI+: 544
382	417	ESI+: 544
383	4	ESI+: 532
384	15	ESI+: 546 NMR1: 0.77-1.05 (5H, m), 1.05-1.34 (5H, m), 1.38-1.55 (1H, m), 1.65-1.91 (4H, m), 2.12-2.24 (3H, m), 2.28-2.40 (1H, m), 2.64-2.85 (1H, m), 3.01-3.18 (2H, m), 3.58-3.76 (8H, m), 4.37-4.62 (1H, m), 6.24-6.39 (1H, m), 7.09-7.17 (1H, m), 7.36-7.90 (5H, m)
385	4,16	ESI+: 558 NMR1: 0.87-0.89 (1H, m), 0.95-1.15 (2H, m), 1.15-1.31 (7H, m), 1.31-1.44 (2H, m), 1.44-1.63 (3H, m), 1.79-2.18 (5H, m), 2.78-2.87 (1H, m), 3.05-3.38 (4H, m), 3.53-3.75 (9H, m), 5.00-5.09 (1H, m), 6.26-6.40 (1H, m), 7.16-7.26 (1H, m), 7.37-7.89 (5H, m), 8.07-8.20 (1H, m)
386	386	ESI+: 562 NMR1: 0.82-1.08 (5H, m), 1.08-1.34 (2H, m), 1.38-1.53 (1H, m), 1.58-1.65 (1H, m), 1.68-1.88 (3H, m), 3.02-3.18 (3H, m), 3.24-3.37 (3H, m), 3.60-3.81 (8H, m), 4.01-4.36 (3H, m), 6.25-6.39 (1H, m), 7.07-7.19 (1H, m), 7.38-7.93 (5H, m)
387	15	ESI+: 486
388	15	ESI+: 500
389	15	ESI+: 486
390	15	ESI+: 500
391	343,16	ESI+: 558
392	343	ESI+: 544
393	343, 16	ESI+: 558 NMR1: 0.81-1.11 (2H, m), 1.12-1.31 (9H, m), 1.31-1.62 (2H, m), 1.80-2.01 (3H, m), 2.04-2.14 (1H, m), 2.75-2.88 (4H, m), 3.04-3.32 (4H, m), 3.32-4.14 (8H, m), 4.41 (1H, s), 6.21-6.37 (1H, m), 7.14-7.26 (1H, m), 7.37-7.88 (5H, m), 8.41-8.54 (1H, m)

[0628] [表 115]

[0629]

Ex	Syn	DATA
394	343	ESI+: 544
395	343	ESI+: 530
396	343	ESI+: 602 NMR1: 0.98-0.97 (3H, m), 1.04 (12H, s), 1.05-1.21 (1H, m), 1.21-1.33 (1H, m), 1.37-1.62 (1H, m), 1.67-1.86 (4H, m), 2.29-2.45 (4H, m), 3.01-3.16 (2H, m), 3.57-3.75 (8H, m), 5.15 (2H, s), 6.23-6.38 (1H, m), 7.07-7.16 (1H, m), 7.37-7.90 (5H, m)
397	26,16	ESI+: 544 NMR1: 0.79-0.90 (1H, m), 0.91-1.20 (2H, m), 1.13 (3H, t, J = 7.6 Hz), 1.22-1.32 (1H, m), 1.35-1.62 (3H, s), 1.79-1.93 (2H, m), 1.95-2.11 (2H, m), 2.64-2.75 (3H, m), 3.05-3.24 (4H, m), 3.28-3.40 (1H, m), 3.44-3.53 (3H, m), 3.59-3.76 (8H, m), 6.25-6.41 (1H, m), 7.15-7.78 (1H, m), 7.38-7.90 (5H, m), 9.54-9.75 (1H, m)
398	343	ESI+: 558 NMR1: 0.81-1.11 (8H, m), 1.11-1.35 (2H, m), 1.40-1.63 (2H, m), 1.67-1.96 (4H, m), 2.14-2.42 (6H, m), 3.03-3.19 (2H, m), 3.19-3.28 (1H, m), 3.58-3.87 (8H, m), 3.87-4.08 (1H, m), 6.23-6.41 (1H, m), 7.06-7.19 (1H, m), 7.34-7.91 (5H, m), 8.31 (1H, s)
399	4	ESI+: 530 NMR1: 0.77-1.04 (8H, m), 1.08-1.33 (1H, m), 1.39-1.61 (1H, m), 1.67-1.96 (4H, m), 2.84-2.97 (1H, m), 3.04-3.20 (4H, m), 3.22 (3H, s), 3.59-3.80 (8H, m), 6.24-6.36 (1H, m), 7.12 (1H, t, J = 5.4 Hz), 7.37-7.90 (5H, m)
400	26,16	ESI+: 586
401	26,16	ESI+: 588 NMR1: 0.79-1.12 (2H, m), 1.16-1.28 (7H, m), 1.33-1.61 (4H, m), 1.81-1.92 (2H, m), 1.92-1.97 (3H, s), 2.00-2.12 (2H, m), 3.06-3.19 (2H, m), 3.28 (6H, s), 3.40-3.50 (2H, m), 3.61-3.75 (11H, m), 3.77-3.89 (1H, m), 4.24-4.64 (1H, m), 6.29-6.43 (1H, m), 7.19-7.30 (1H, m), 7.38-7.94 (5H, m), 8.29-8.46 (1H, m)

[0630] [表 116]

[0631]

Ex	Syn	DATA
402	4,16	ESI+: 572 NMR1: 0.80-1.14 (2H, m), 1.14-1.30 (11H, m), 1.30-1.46 (1H, m), 1.46-1.65 (2H, m), 1.79-1.93 (2H, m), 1.93-2.13 (3H, m), 2.77-2.88 (1H, m), 3.03-3.33 (7H, m), 3.41-3.98 (5H, m), 4.05-4.34 (2H, m), 4.34-4.78 (1H, m), 6.23-6.36 (1H, m), 7.16-7.29 (1H, m), 7.38-7.92 (5H, m), 8.22-8.41 (1H, m)
403	4,16	ESI+: 572 NMR1: 0.96-1.12 (2H, m), 1.12-1.31 (12H, m), 1.31-1.47 (1H, m), 1.47-1.63 (2H, m), 1.79-1.93 (2H, m), 1.94-2.22 (2H, m), 2.75-2.89 (1H, m), 3.05-3.34 (4H, m), 3.39-3.98 (5H, m), 4.04-4.60 (5H, m), 6.23-6.37 (1H, m), 7.19-7.32 (1H, m), 7.38-7.93 (5H, m), 8.29-8.47 (1H, m)
404	26,16	ESI+: 584
405	386	ESI+: 562
406	1	ESI+: 588
407	1	ESI+: 458
408	1	ESI+: 590
409	1	ESI+: 586
410	289	ESI+: 488
411	2	ESI+: 543
412	289	ESI+: 490
413	289	ESI+: 486
414	1	ESI+: 459
415	4,16	ESI+: 612
416	23	ESI+: 558
417	417	ESI+: 486 NMR1: 1.15-1.36 (3H, m), 1.24 (3H, d, J = 6.7 Hz), 1.46-1.60 (2H, m), 1.95-2.16 (4H, m), 2.68 (3H, s), 2.69 (3H, s), 3.04-3.25 (2H, m), 3.40-4.16 (5H, m), 4.35-4.45 (1H, m), 6.31 (1H, s), 6.98-7.98 (6H, m)
418	23	ESI+: 556
419	23	ESI+: 560
420	417	ESI+: 487

[0632] [表 117]

[0633]

Ex	Syn	DATA
421	2	ESI+: 544
422	26	ESI+: 496 NMR1: 0.78-1.05 (4H, m), 1.05-1.30 (1H, m), 1.40-1.62 (1H, m), 1.68-1.95 (4H, m), 2.97-3.48 (4H, m), 3.55-3.73 (8H, m), 6.24-6.38 (1H, m), 7.12 (1H, t, J = 4 Hz), 7.37-7.88 (5H, m)
423	26	ESI+: 534 NMR1: 0.82-1.01 (2H, m), 1.07-1.30 (2H, m), 1.39-1.57 (1H, m), 1.72-1.96 (4H, m), 2.35-2.46 (1H, m), 3.03-3.50 (8H, m), 3.55-3.74 (8H, m), 6.24-6.37 (1H, m), 7.1-7.17 (1H, m), 7.37-7.89 (5H, m)
424	4	ESI+: 514 NMR1: 0.83-1.01 (8H, m), 1.08-1.23 (2H, m), 1.38-1.53 (1H, m), 1.65-1.86 (4H, m), 3.03-3.18 (2H, m), 3.59-3.73 (8H, m), 6.23-6.38 (1H, m), 7.09-7.15 (1H, m), 7.36-7.88 (5H, m)
425	343	ESI+: 590
426	4,16	ESI+: 626
427	4	ESI+: 572
428	26	ESI+: 528
429	26	ESI+: 514
430	26	ESI+: 568 NMR1: 0.79-0.99 (2H, m), 0.99-1.09 (6H, m), 1.09-1.29 (1H, m), 1.39-1.60 (1H, m), 1.65-1.90 (4H, m), 2.32-2.41 (2H, m), 2.96 (1H, s), 3.02-1.89 (2H, m), 3.49 (2H, s), 3.59-3.75 (8H, m), 4.01 (1H, s), 6.25-6.38 (1H, m), 7.08-7.16 (1H, m), 7.38-7.89 (5H, m)
431	1	ESI+: 458
432	2	ESI+: 543
433	433	ESI+: 516
434	15	ESI+: 544 NMR1: 0.83-1.02 (6H, m), 1.10-1.28 (2H, m), 1.38-1.53 (1H, m), 1.67-1.83 (4H, m), 2.13 (3H, s), 2.87-2.98 (1H, m), 3.03-3.16 (3H, m), 3.21 (3H, s), 3.59-3.76 (8H, m), 6.25-6.37 (1H, m), 7.08-7.16 (1H, m), 7.37-7.89 (5H, m)

[0634] [表 118]

[0635]

Ex	Syn	DATA
435	4	ESI+: 558 NMR1: 0.83-1.05 (8H, m), 1.11-1.31 (2H, m), 1.40-1.52 (1H, m), 1.55-1.84 (3H, m), 2.92-3.16 (3H, m), 3.19-3.26 (3H, m), 3.28-3.29 (1H, m), 3.59-3.73 (8H, m), 6.25-6.37 (1H, m), 7.08-7.14 (1H, m), 7.37-7.89 (5H, m)
436	436	ESI+: 527
437	26	ESI+: 582
438	26,16	ESI+: 582 NMR1: 0.96-1.12 (2H, m), 1.25-1.35 (3H, m), 1.45-1.69 (3H, m), 1.81-1.92 (5H, m), 1.94-2.01 (1H, m), 2.01-2.16 (1H, m), 3.06-3.21 (2H, m), 3.28-3.40 (3H, m), 3.44-3.51 (1H, m), 3.57 (2H, s), 3.60-3.75 (8H, m), 3.81-3.94 (1H, m), 3.99-4.12 (2H, m), 6.31-6.42 (1H, m), 7.2-7.35 (1H, m), 7.38-7.91 (5H, m), 9.61-9.99 (1H, m)
439	439	ESI+: 556
440	439	ESI+: 542
441	26,16	ESI+: 598 NMR1: 0.91-1.12 (2H, m), 1.18-1.29 (6H, m), 1.32-1.63 (3H, m), 1.68-1.93 (5H, m), 1.96 (2H, s), 2.00-2.17 (4H, m), 2.64-2.74 (1H, m), 3.04-3.20 (3H, m), 3.22-3.35 (3H, m), 3.61-3.77 (8H, m), 6.32-6.47 (1H, m), 7.25-7.94 (6H, m), 8.61-8.81 (1H, m)
442	26	ESI+: 570 NMR1: 0.80-0.97 (2H, m), 1.03 (6H, s), 1.09-1.30 (2H, m), 1.40-1.60 (1H, m), 1.68-1.87 (4H, m), 2.25-2.30 (2H, m), 3.02-3.15 (1H, m), 3.15-3.22 (1H,), 3.60-3.73 (8H, m), 3.87 (1H, s), 4.95 (1H, d, J = 9,6 Hz), 5.12 (1H, d, J = 17 Hz), 5.73-5.84 (1H, m), 6.24-6.38 (1H, m), 7.07-7.14 (1H, m), 7.38-7.88 (5H, m)
443	1	ESI+: 572
444	4	ESI+: 544
445	15	ESI+: 558

[0636] [表 119]

[0637]

Ex	Syn	DATA
446	4	ESI+: 544 NMR1: 0.79-1.00 (4H, m), 0.91 (3H, d, J = 10.4 Hz), 1.07-1.17 (1H, m), 1.23 (3H, d, J = 7.6 Hz), 1.40-1.57 (1H, m), 1.68-1.93 (4H, m), 2.35-2.44 (1H, m), 2.86-2.94 (1H, m), 3.02-3.20 (3H, m), 3.22 (3H, s), 3.40-3.52 (2H, m), 3.58-3.75 (2H, m), 3.89-4.12 (2H, m), 4.34-4.47 (1H, m), 6.20-6.31 (1H, m), 7.07-7.17 (1H, m), 7.37-7.89 (5H, m)
447	15	ESI+: 558 NMR1: 0.82-1.03 (3H, m), 0.93 (3H, d, J = 7.2 Hz), 1.10-1.29 (2H, m), 1.23 (3H, d, J = 8 Hz), 1.39-1.55 (1H, m), 1.67-1.89 (4H, m), 2.14 (3H, s), 2.33-2.42 (1H, m), 2.87-2.98 (1H, m), 3.02-3.19 (3H, m), 3.21 (3H, s), 3.41.3.53 (2H, m), 3.58-3.75 (2H, m), 3.89-4.14 (2H, m), 4.34-4.49 (1H, m), 6.20-6.31 (1H, m), 7.07-7.17 (1H, m), 7.37-7.90 (5H, m)
448	26,16	ESI+: 596
449	26	ESI+: 598 NMR1: 0.76-0.97 (2H, m), 1.02 (6H, s), 1.07-1.31 (2H, m), 1.36-1.53 (1H, m), 1.58 (3H, s), 1.66 (3H, s), 1.66-1.86 (4H, m), 2.24 (2H, s), 2.37-2.50 (1H, m), 3.01-3.17 (4H, m), 3.58-3.75 (8H, m), 3.85 (1H, s), 5.13-5.20 (1H, m), 6.24-6.38 (1H, m), 7.07-7.16 (1H, m), 7.37-7.90 (5H, m)
450	4,16	ESI+: 542 NMR1: 0.77-1.11 (2H, m), 0.81 (6H, t, J = 7.2 Hz), 1.07-1.23 (1H, m), 1.23-1.40 (3H, m), 1.40-1.54 (1H, m), 1.62-1.74 (2H, m), 1.74-1.88 (2H, m), 2.27-2.43 (4H, m), 3.01-3.18 (2H, m), 3.58-3.75 (8H, m), 6.24-6.37 (1H, m), 7.07-7.15 (1H, m), 7.36-7.89 (5H, m)
451	1	ESI+: 588
452	289	ESI+: 488
453	10	ESI+: 558
454	295	ESI+: 556
455	295	ESI+: 542
456	295	ESI+: 556 NMR1: 0.82-1.03 (1H, m), 1.07-1.30 (1H, m), 1.36-1.72 (9H, m), 1,72-1.94 (2H, m), 2.37-2.46 (1H, m), 2.64-3.03 (5H, m), 3.12-3.27 (4H, m), 3.59-3.77 (8H, m), 6.24-6.38 (1H, m), 7.06-7.19 (1H, m), 7.37-7.89 (5H, m)

[0638] [表 120]

[0639]

Ex	Syn	DATA
457	2	ESI+: 602
458	2	ESI+: 616
459	289	ESI+: 502
460	289	ESI+: 516
461	295	ESI+: 530 NMR1: 0.80-2.18 (12H, m), 2.29-2.39 (1H, m), 2.54-2.70 (1H, m), 2.75-2.92 (2H, m), 3.18-3.29 (2H, m), 3.59-3.73 (8H, m), 5.05-5.26 (1H, m), 6.14 (1H, s), 7.36-7.66 (4H, m), 7.70-7.75 (1H, m), 7.83-7.88 (1H, m)
462	295	ESI+: 530
463	343	ESI+: 531
464	1	ESI+: 590
465	26	ESI+: 580
466	26,16	ESI+: 594
467	289	ESI+: 490
468	23	ESI+: 560
469	295	ESI+: 531
470	295	ESI+: 531
471	4	ESI+: 572 NMR1: 0.78-1.17 (17H, m), 1.17-1.40 (2H, m), 1.40-1.61 (2H, m), 1.68-1.90 (4H, m), 3.01-3.19 (2H, m), 3.58-3.75 (8H, m), 4.00-4.40 (1H, m), 6.23-6.38 (1H, m), 7.05-7.17 (1H, m), 7.37-7.88 (5H, m)
472	4	ESI+: 572
473	12	ESI+: 556 NMR-CDCl3: 1.35-1.49 (2H, m), 1.60-1.74 (2H, m), 1.77-1.86 (4H, m), 2.07-2.26 (4H, m), 2.56-2.65 (4H, m), 3.14 (2H, s), 3.75-3.83 (8H, m), 3.83-4.00 (1H, m), 5.01-5.12 (1H, m), 6.22 (1H, s), 7.02-7.09 (1H, m), 7.25 (1H, t, J = 53 Hz), 7.36-7.45 (2H, m), 7.65-7.72 (1H, m), 7.85-7.93 (1H, m)
474	12	ESI+: 572
475	12	ESI+: 588
476	12	ESI+: 614
477	12	ESI+: 600

[0640] [表 121]

[0641]

Ex	Syn	DATA
478	12	ESI+: 574
479	12	ESI+: 574
480	295	ESI+: 556
481	13,16	ESI+: 582 NMR1: 0.80-1.34 (14H, m), 1.48-1.64 (1H, m), 1.67-1.85 (2H, m), 1.85-2.12 (3H, m), 2.69 (1H, s), 2.93-3.21 (3H, m), 3.25-3.25 (1H, m), 3.60-3.81 (8H, m), 4.29-4.42 (2H, m), 5.14-5.36 (1H, m), 6.46 (1H, s), 7.32-7.89 (6H, m), 7.96-8.14 (1H, m)
482	295	ESI+: 545 NMR1: 0.99-1.93 (13H, m), 2.39-2.56 (2H, m), 2.80-2.88 (1H, m), 3.03-3.14 (1H, m), 3.63-3.80 (8H, m), 3.94-4.28 (4H, m), 6.42 (1H, s), 7.39-7.69 (3H, m), 7.73-7.89 (1H, m), 7.83-7.90 (1H, m)
483	295	ESI+: 545 NMR1: 1.43-1.81 (12H, m), 1.92-2.04 (1H, m), 2.39-2.60 (2H, m), 2.81-2.90 (1H, m), 2.98-3.10 (1H, m), 3.63-3.81 (8H, m), 3.96-4.38 (4H, m), 6.43 (1H, s), 7.39-7.68 (3H, m), 7.74-7.79 (1H, m), 7.84-7.89 (1H, m)
484	295,16	ESI+: 544 NMR1: 0.98-1.15 (2H, m), 1.38-1.69 (3H, m), 1.71-2.25 (8H, m), 2.97-3.90 (13H, m), 4.00-4.18 (1H, m), 4.61-4.90 (2H, m), 6.16 (1H, s), 7.37-7.76 (5H, m), 7.83-7.88 (1H, m)
485	295,16	ESI+: 544 NMR1: 1.45-2.17 (13H, m), 3.18-3.33 (2H, m), 3.35-4.50 (12H, m), 4.61-4.92 (2H, m), 6.17 (1H, s), 7.36-7.76 (5H, m), 7.83-7.88 (1H, m)
486	295,16	ESI+: 571
487	295	ESI+: 570
488	26, 16	ESI+: 545 NMR1: 0.80-3.34 (21H, m), 3.58-3.86 (8H, m), 4.194.28 (2H, m), 6.43 (1H, s), 7.38-7.69 (3H, m), 7.72-7.78 (1H, m), 7.84-7.90 (1H, m)

[0642] [表 122]

[0643]

Ex	Syn	DATA
489	10	ESI+: 517
490	295,16	ESI+: 570 NMR1: 0.85-1.08 (1H, m), 1.08-1.32 (6H, m), 1.37-2.08 (10H, m), 2.12-2.28 (1H, m), 3.01-3.29 (2H, m), 3.55-3.80 (8H, m), 5.06-5.39 (1H, m), 6.27-6.40 (1H, m), 7.13-7.23 (1H, m), 7.37-7.97 (5H, m), 8.41-8.66 (1H, m)
491	26,16	ESI+: 584 NMR1: 0.84-1.11 (2H, m), 1.15-1.28 (10H, m), 1.32-1.47 (1H, m), 1.47-1.63 (2H, m), 1.79-1.93 (2H, m), 1.96 (3H, s), 1.96-2.12 (2H, m), 3.02-3.25 (3H, m), 3.25-3.34 (1H, m), 3.41-3.51 (1H, m), 3.55-3.64 (3H, m), 3.69-3.99 (3H, m), 4.34-4.49 (1H, m), 5.47 (1H, d, J = 10.4 Hz), 5.54 (1H, d, J = 8.0 Hz), 6.02-6.17 (1H, m), 6.24-6.35 (1H, m), 7.18-7.27 (1H, m), 7.38-7.90 (5H, m), 8.65-8.81 (1H, m)
492	26,16	ESI+: 584 NMR1: 0.88-1.15 (1H, m), 1.15-1.31 (7H, m), 1.44-1.68 (3H, m), 1.79-1.93 (2H, m), 1.96 (3H, s), 1.96-2.12 (2H, m), 3.03-3.27 (2H, m), 3.31 (3H, s), 3.55-4.14 (8H, m), 4.35-4.48 (1H, m), 5.38-5.59 (2H, m), 5.92-6.08 (1H, m), 6.23-6.34 (1H, m), 7.13-7.24 (1H, m), 7.37-7.91 (5H, m), 8.70-8.94 (1H, m)
493	23	ESI+: 531
494	343	ESI+: 530
495	23	ESI+: 544 NMR1: 0.98-1.15 (2H, m), 1.25 (6H, s), 1.35-1.64 (3H, m), 1.85-1.96 (2H, m), 1.98-2.19 (2H, m), 2.76-2.88 (4H, m), 3.07-3.33 (4H, m), 3.58-3.77 (8H, m), 6.18 (1H, s), 7.37-7.90 (6H, m)
496	10	ESI+: 516 NMR1: 0.89-1.06 (4H, m), 1.42-1.57 (1H, m), 1.71-1.95 (4H, m), 2.25-2.36 (1H, m), 2.64-2.70 (2H, m), 3.19-3.38 (7H, m), 3.61-3.72 (8H, m), 6.14 (1H, s), 7.37-7.67 (4H, m), 7.70-7.74 (1H, m), 7.83-7.88 (1H, m)

[0644] [表 123]

[0645]

Ex	Syn	DATA
497	23	ESI+: 530 NMR1: 0.98-1.15 (2H, m), 1.38-1.62 (3H, m), 1.84-1.96 (2H, m), 1.98-2.14 (2H, m), 2.65-2.73 (3H, m), 3.09-3.42 (8H, m), 3.61-3.75 (10H, m), 6.17 (1H, s), 7.37-7.76 (5H, m), 7.83-7.88 (1H, m)
498	2	ESI+: 556
499	9,16	ESI+: 558 NMR1: 0.92-1.27 (5H, m), 1.43-1.62 (3H, m), 1.62-1.71 (1H, m), 1.75-1.88 (2H, m), 3.05-3.22 (4H, m), 3.27 (3H, s), 4.40-3.52 (1H, m), 3.60-3.71 (8H, m), 3.98-4.09 (2H, m), 6.26-6.39 (1H, m), 7.12-7.25 (1H, m), 7.37-7.87 (5H, m)
500	2	ESI+: 556 NMR1: 1.41-1.74 (7H, m), 1.79-1.89 (2H, m), 1.98-2.18 (3H, m), 2.20-2.29 (4H, m), 2.63-2.71 (1H, m), 2.97-3.05 (1H, m), 3.58-3.80 (9H, m), 4.99-5.11 (1H, m), 6.39 (1H, s), 7.38-7.69 (4H, m), 7.72-7.79 (1H, m), 7.83-7.89 (1H, m)
501	2	ESI+: 545
502	4	ESI+: 558
503	4	ESI+: 558
504	4	ESI+: 544
505	15	ESI+: 572 NMR1: 0.80-1.02 (10H, m), 1.02 (3H, s), 1.14 (3H, s), 1.14-1.33 (1H, m), 1.23 (3H, d, J = 6.4 Hz), 1.39-1.70 (1H, m), 1.73-1.87 (3H, m), 2.19 (2H, s), 3.02-3.23 (2H, m), 3.38-3.51 (1H, m), 3.58-3.77 (2H, m), 3.89-3.96 (1H, m), 3.99-4.45 (2H, m), 6.20-6.32 (1H, m), 7.06-7.19 (1H, m), 7.37-7.90 (5H, m)
506	15	ESI+: 572 NMR1: 0.81-1.02 (10H, m), 1.02 (3H, s), 1.14 (3H, s), 1.14-1.33 (1H, m), 1.23 (3H, d, J = 6.4 Hz), 1.39-1.70 (1H, m), 1.73-1.87 (3H, m), 2.20 (2H, s), 3.01-3.23 (2H, m), 3.38-3.51 (1H, m), 3.58-3.77 (2H, m), 3.89-3.96 (1H, m), 3.99-4.45 (2H, m), 6.21-6.31 (1H, m), 7.06-7.17 (1H, m), 7.37-7.87 (5H, m)

[0646] [表 124]

[0647]

Ex	Syn	DATA
507	15	ESI+: 558 NMR1: 0.82-1.03 (3H, m), 0.93 (3H, d, J = 6 Hz), 1.09-1.27 (2H, m), 1.23 (3H, d, J = 5.6 Hz), 1.39-1.53 (1H, m), 1.66-1.85 (4H, m), 2.14 (3H, s), 2.33-2.41 (1H, m), 2.87-2.98 (1H, m), 3.01-3.21 (3H, m), 3.21 (3H, s), 3.40-3.52 (1H, m), 3.58-3.65 (1H, m), 3.65-3.77 (1H, m), 3.89-3.97 (1H, m), 4.01-4.13 (1H, m), 4.35-4.47 (1H, m), 6.19-6.32 (1H, m), 7.06-7.18 (1H, m), 7.37-7.89 (5H, m)
508	4	ESI+: 572 NMR1: 0.82-1.05 (9H, m), 1.23-1.33 (2H, m), 1.23 (3H, d, J = 6.4 Hz), 1.39-1.53 (1H, m), 1.56-1.65 (1H, m), 1.66-1.84 (3H, m), 1.92-2.01 (1H, m), 2.01-2.12 (2H, m), 3.12-3.28 (2H, m), 3.21 (3H, s), 3.40-3.51 (1H, m), 3.58-3.65 (1H, m), 3.65-3.77 (1H, m), 3.89-3.97 (1H, m), 4.01-4.13 (1H, m), 4.34-4.47 (1H, m), 6.20-6.32 (1H, m), 7.06-7.18 (1H, m), 7.37-7.89 (5H, m)
509	4	ESI+: 544
510	295,16	ESI+: 544 NMR1: 1.45-1.59 (2H, m), 1.66-2.02 (10H, m), 2.04-2.17 (1H, m), 3.19-3.32 (2H, m), 3.35-3.55 (3H, m), 3.60-376 (8H, m), 4.02-4.21 (2H, m), 4.59-4.95 (1H, m), 6.18 (1H, s), 7.37-7.76 (5H, m), 7.89-7.88 (1H, m)
511	295,16	ESI+: 544 NMR1: 0.97-1.16 (2H, m), 1.40-1.65 (3H, m), 1.69-2.00 (5H, m), 2.02-2.15 (2H, m), 2.17-2.28 (1H, m), 3.02-4.17 (15H, m), 4.61-4.96 (1H, m), 6.18 (1H, s), 7.36-7.89 (6H, m)
512	295,16	ESI+: 556 NMR1: 1.44-1.58 (2H, m), 1.64-2.11 (11H, m), 3.05-3.98 (19H, m), 6.19 (1H, s), 7.37-7.90 (6H, m)
513	295,16	ESI+: 556 NMR1: 0.97-1.16 (2H, m), 1.37-1.63 (3H, m), 1.66-1.78 (1H, m), 1.80-1.96 (4H, m), 1.97-2.11 (2H, m), 2.13-2.30 (1H, m), 3.00-4.00 (19H, m), 6.16 (1H, s), 7.37-7.76 (5H, m), 7.83-7.89 (1H, m)

[0648] [表 125]

[0649]

Ex	Syn	DATA
514	295	ESI+: 544 NMR1: 0.80-1.22 (1H, m), 1.22-1.90 (14H, m), 2.70-2.92 (1H, m), 2.92-3.10 (1H, m), 3.16-3.29 (1H, m), 3.57-3.81 (8H, m), 3.91-4.31 (2H, m), 6.24-6.38 (1H, m), 7.06-7.19 (1H, m), 7.37-7.90 (5H, m)
515	295	ESI+: 544 NMR1: 0.81-1.29 (5H, m), 1.38-1.99 (10H, m), 2.78-2.86 (1H, m), 3.00-3.19 (2H, m), 3.58-3.76 (8H, m), 3.92-4.27 (2H, m), 6.25-6.39 (1H, m), 7.08-7.19 (1H, m), 7.37-7.91 (5H, m)
516	2	ESI+: 544
517	2	ESI+: 558 NMR1: 0.74 (3H, d, J = 7.2 Hz), 0.87 (3H, d, J = 6.4 Hz), 0.92-1.08 (1H, m), 1.12-1.32 (4H, m), 1.41-1.58 (1H, m), 1.67-1.83 (4H, m), 1.89-1.98 (1H, m), 3.03-3.20 (2H, m), 3.26-3.47 (1H, m), 3.47-3.58 (1H, m), 3.58-3.77 (8H, m), 6.26-6.39 (1H, m), 7.12-7.21 (1H, m), 7.35-7.95 (5H, m)
518	13,16	ESI+: 584 NMR1: 0.79-1.37 (11H, m), 1.44-1.65 (1H, m), 1.65-1.85 (2H, m), 1.85-1.97 (1H, m), 1.97-2.21 (3H, m), 2.91-3.15 (2H, m), 3.31-3.53 (4H, m), 3.60-3.77 (8H, m), 4.14-4.26 (1H, m), 5.03-5.33 (2H, m), 5.84-6.00 (1H, m), 6.36-6.47 (1H, m), 7.24-8.03 (6H, m), 8.12-8.42 (1H, m)
519	4	ESI+: 560
520	295,16	ESI+: 598
521	295,16	ESI+: 598
522	295,16	ESI+: 570
523	295,16	ESI+: 570
524	295,16	ESI+: 526
525	295,16	ESI+: 526 NMR1: 1.00-2.19 (16H, m), 2.87-4.42 (14H, m), 6.15 (1H, m), 7.37-7.76 (5H, m), 7.83-7.89 (1H, m)
526	295,16	ESI+: 595

[0650] [表 126]

[0651]

Ex	Syn	DATA
527	295,16	ESI+: 595 NMR1: 0.99-1.30 (2H, m), 1.41-1.66 (3H, m), 1.80-2.38 (12H, m), 2.95-3.12 (2H, m), 3.17-4.15 (18H, m), 6.16 (1H, s), 7.37-7.76 (5H, m), 7.83-7.88 (1H, m)
528	295,16	ESI+: 560
529	295,16	ESI+: 560
530	295,16	ESI+: 560
531	295,16	ESI+: 560 NMR1: 0.92-1.29 (2H, m), 1.36-1.71 (3H, m), 1.78-2.08 (3H, m), 2.14-2.29 (1H, m), 3.02-4.47 (18H, m), 4.68-5.28 (2H, m), 6.16 (1H, m), 7.37-7.77 (5H, m), 7.83-7.89 (1H, m)
532	295,16	ESI+: 572
533	295,16	ESI+: 572
534	295,16	ESI+: 572
535	295,16	ESI+: 572 NMR1: 0.97-1.27 (2H, m), 1.36-1.69 (3H, m), 1.84-2.14 (4H, m), 3.00-4.22 (23H, m), 6.16 (1H, s), 7.36-7.78 (5H, m), 7.82-7.91 (1H, m)
536	295,16	ESI+: 530
537	295,16	ESI+: 530
538	295,16	ESI+: 530
539	295,16	ESI+: 530 NMR1: 0.89-1.09 (2H, m), 1.13-1.35 (2H, m), 1.45-1.58 (1H, m), 1.81-1.99 (3H, m), 2.01-2.13 (1H, m), 2.16-2.39 (2H, m), 3.00-5.05 (16H, m), 6.15 (1H, s), 7.37-7.76 (5H, m), 7.83-7.89 (1H, m)
540	540	ESI+: 570
541	10	ESI+: 602
542	542	ESI+: 570
543	12	ESI+: 558
544	12	ESI+: 574
545	295,16	ESI+: 542
546	295,16	ESI+: 542

[0652] [表 127]

[0653]

Ex	Syn	DATA
547	26,16	ESI+: 526
548	26,16	ESI+: 540
549	26	ESI+: 584
550	433,16	ESI+: 516
551	554	ESI+: 572
552	26	ESI+: 558
553	10	ESI+: 530
554	554	ESI+: 558
555	555	ESI+: 542
556	2	ESI+: 658
557	2	ESI+: 660
558	2	ESI+: 658
559	2	ESI+: 660
560	295,16	ESI+: 574
561	295,16	ESI+: 574
562	295,16	ESI+: 662
563	295,16	ESI+: 662
564	295,16	ESI+: 650
565	295,16	ESI+: 650
566	289	ESI+: 558
567	289	ESI+: 560
568	289	ESI+: 558
569	289	ESI+: 560
570	570	ESI+: 590
571	570	ESI+: 591
572	570	ESI+: 590
573	12	ESI+: 581 NMR1: 1.26-1.40 (3H, m), 1.55-1.87 (10H, m), 2.04-2.15 (3H, m), 2.74-2.81 (2H, m), 3.08-3.42 (3H, m), 3.62-3.85 (10H, m), 6.10 (1H, s), 7.38-7.95 (6H, m)

[0654] [表 128]

[0655]

Ex	Syn	DATA
574	12	ESI+: 555 NMR1: 0.82-1.41 (3H, m), 1.53-1.85 (4H, m), 1.95-2.14 (3H, m), 2.23 (6H, s), 3.11-3.38 (3H, m), 3.60-3.87 (10H, m), 6.10 (1H, s), 7.38-7.64 (4H, m), 7.70-7.73 (1H, m), 7.83-7.87 (1H, m)
575	12	ESI+: 582 NMR1: 1.48-1.89 (12H, m), 2.05-2.25 (3H, m), 2.74-2.83 (2H, m), 3.11-3.39 (3H, m), 3.65-3.88 (10H, m), 5.01-5.07 (1H, m), 6.40 (1H, s), 7.40-7.67 (3H, m), 7.73-7.76 (1H, m), 7.85-7.88 (1H, m)
576	12	ESI+: 556 NMR1: 1.45-2.23 (8H, m), 2.24 (6H, s), 3.08-3.44 (4H, m), 3.62-3.90 (10H, m), 4.99-5.08 (1H, m), 6.40 (1H, s), 7.40-7.67 (3H, m), 7.73-7.76 (1H, m), 7.85-7.88 (1H, m)
577	12	ESI+: 581 NMR1: 1.27-1.68 (10H, m), 1.74-2.15 (4H, m), 2.43-2.85 (4H, m), 3.08-3.39 (3H, m), 3.59-3.78 (10H, m), 3.27-3.37 (1H, m), 6.92-7.04 (1H, m), 7.36-7.91 (5H, m)
578	12	ESI+: 555 NMR1: 1.23-2.10 (10H, m), 2.22 (6H, s), 3.07-3.42 (2H, m), 3.56-3.83 (10H, m), 3.26-3.38 (1H, m), 6.92-7.05 (1H, m), 7.36-7.88 (6H, m)
579	3	ESI+: 556 [M+Na]
580	554,16	ESI+: 558
581	21	ESI+: 572
582	21	ESI+: 574
583	21	ESI+: 572
584	21	ESI+: 574 NMR1: 1.37-1.71 (4H, m), 1.86-2.02 (2H, m), 2.05-2.26 (2H, m), 2.66-2.97 (4H, m), 3.36-3.84 (11H, m), 3.94-4.13 (1H, m), 4.30-4.44 (1H, m), 5.01-5.13 (1H, m), 5.33-5.56 (1H, m), 6.40 (1H, s), 7.38-7.69 (3H, m), 7.71-7.77 (1H, m), 7.83-7.89 (1H, m), 8.86-8.98 (1H, m)

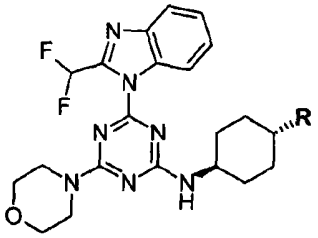
[0656] [表 129]

[0657]

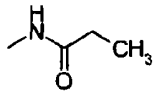
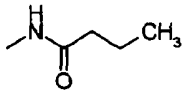
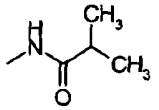
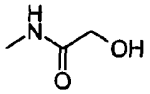
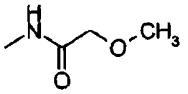
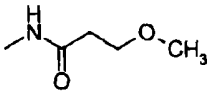
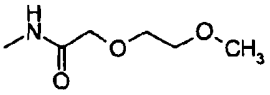
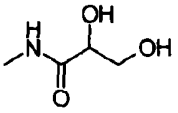
Ex	Syn	DATA
585	22	ESI+ :467
586	22	ESI+ :580[M+Na]
587	8	ESI+ :472
588	1	ESI+ :594[M+Na]

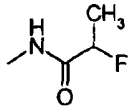
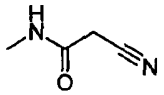
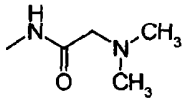
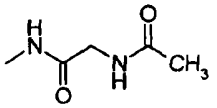
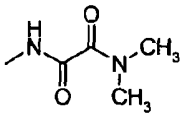
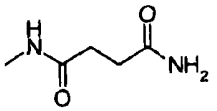
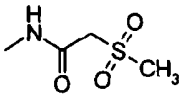
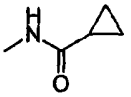
589	2	ESI+:557
590	22	ESI+:499
591	1	ESI+:499

[0658] [表 130]



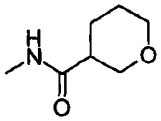
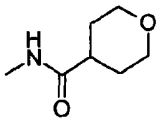
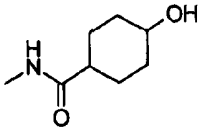
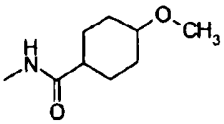
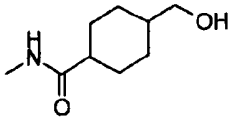
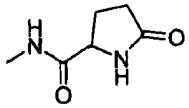
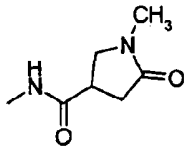
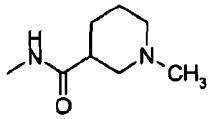
[0659]

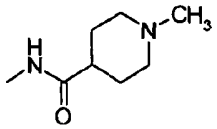
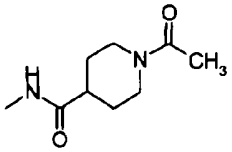
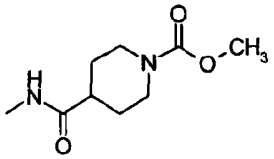
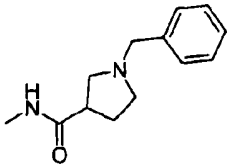
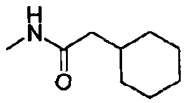
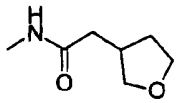
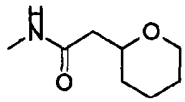
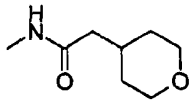
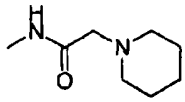
Ex	R
A1	
A2	
A3	
A4	
A5	
A6	
A7	
A8	

Ex	R
A9	
A10	
A11	
A12	
A13	
A14	
A15	
A16	

[0660] [表 131]

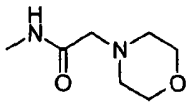
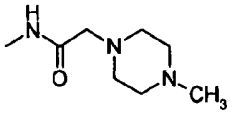
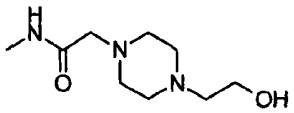
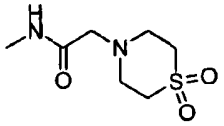
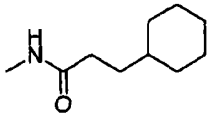
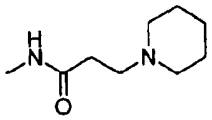
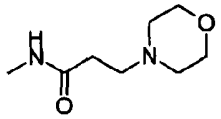
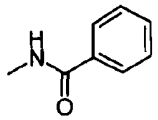
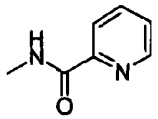
[0661]

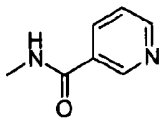
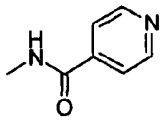
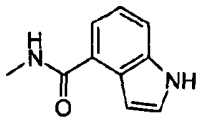
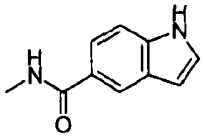
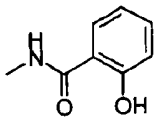
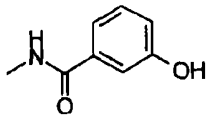
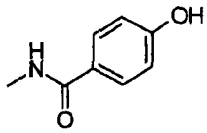
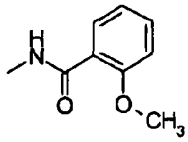
Ex	R
A17	
A18	
A19	
A20	
A21	
A22	
A23	
A24	

Ex	R
A25	
A26	
A27	
A28	
A29	
A30	
A31	
A32	
A33	

[0662] [表 132]

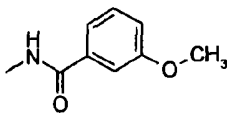
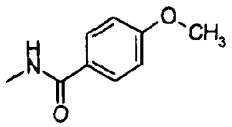
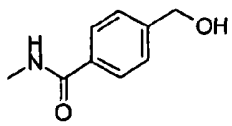
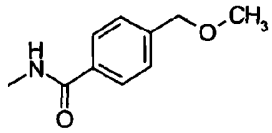
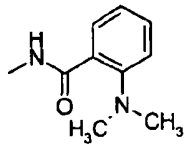
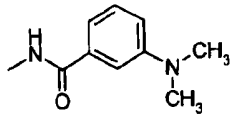
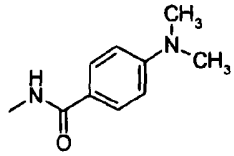
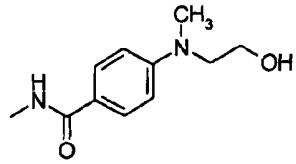
[0663]

Ex	R
A34	
A35	
A36	
A37	
A38	
A39	
A40	
A41	
A42	

Ex	R
A43	
A44	
A45	
A46	
A47	
A48	
A49	
A50	

[0664] [表 133]

[0665]

Ex	R
A51	
A52	
A53	
A54	
A55	
A56	
A57	
A58	

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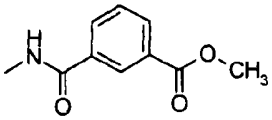
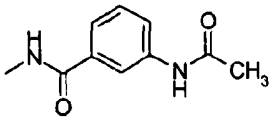
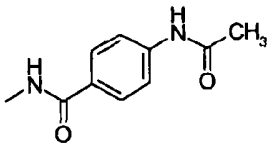
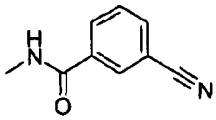
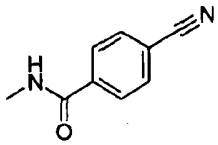
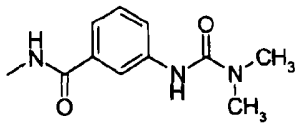
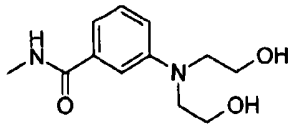
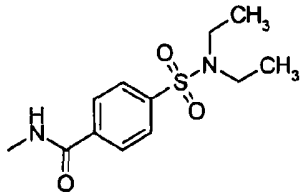
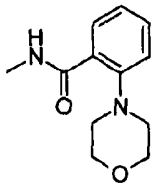
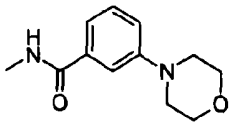
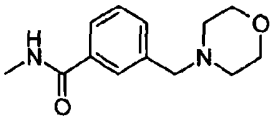
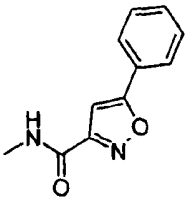
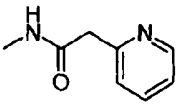
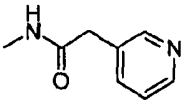
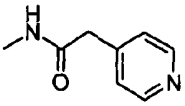
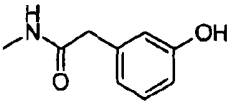
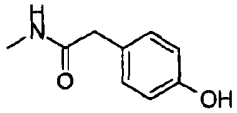
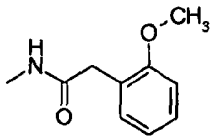
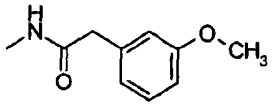
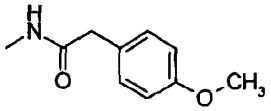
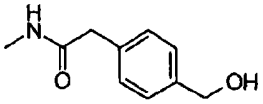
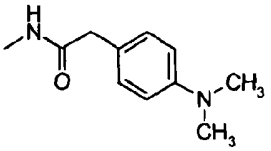
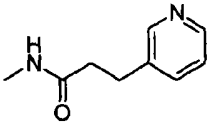
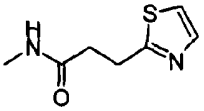
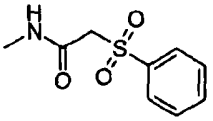
A59	
A60	
A61	
A62	
A63	
A64	
A65	
A66	

[0666] [表 134]

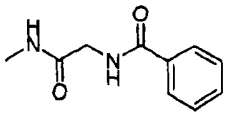
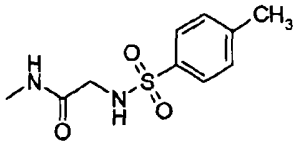
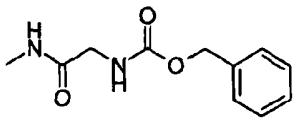
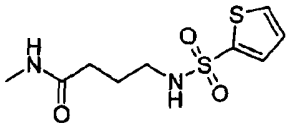
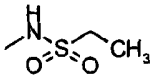
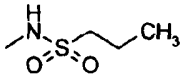
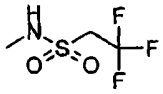
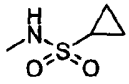
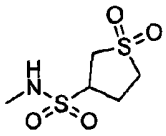
[0667]

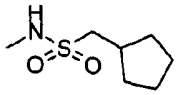
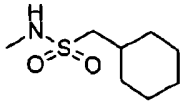
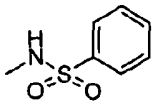
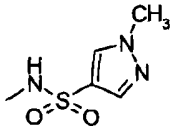
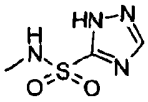
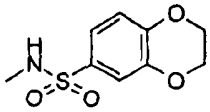
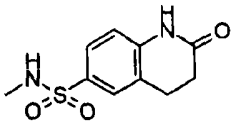
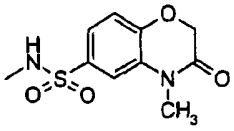
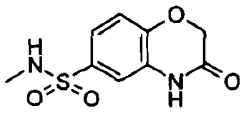
Ex	R
A67	
A68	
A69	
A70	
A71	
A72	
A73	
A74	

Ex	R
A75	
A76	
A77	
A78	
A79	
A80	
A81	
A82	
A83	

[0668] [表 135]

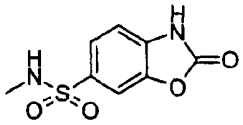
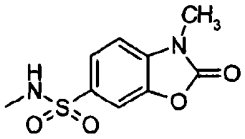
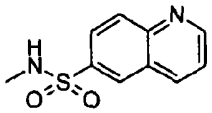
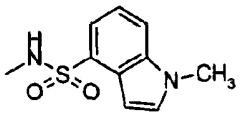
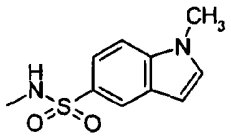
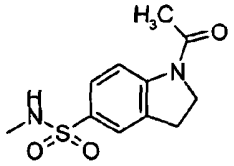
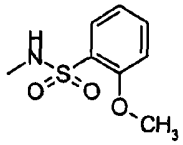
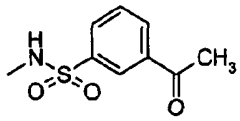
[0669]

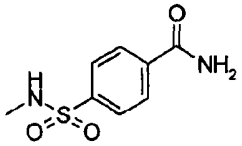
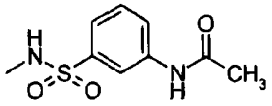
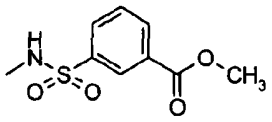
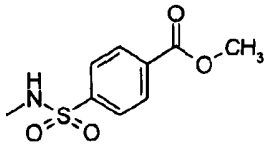
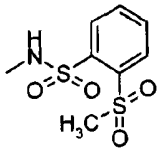
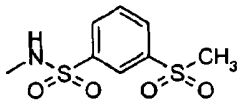
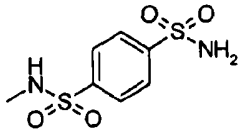
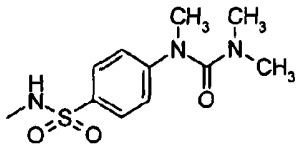
Ex	R
A84	
A85	
A86	
A87	
B1	
B2	
B3	
B4	
B5	

Ex	R
B6	
B7	
B8	
B9	
B10	
B11	
B12	
B13	
B14	

[0670] [表 136]

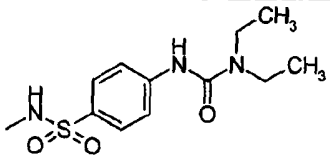
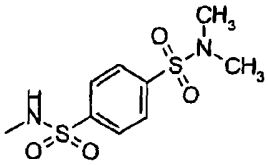
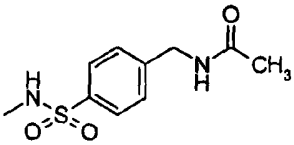
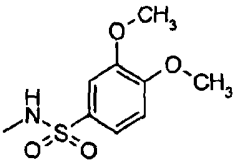
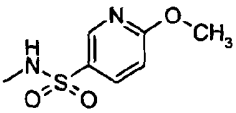
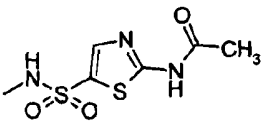
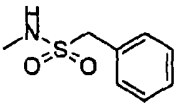
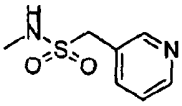
[0671]

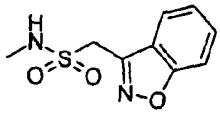
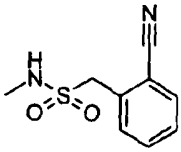
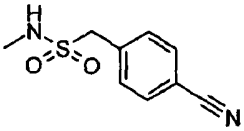
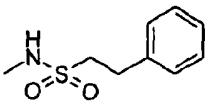
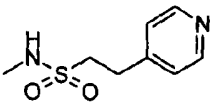
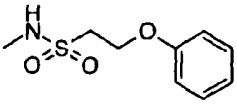
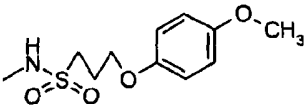
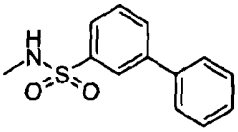
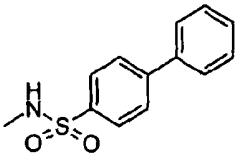
Ex	R
B15	
B16	
B17	
B18	
B19	
B20	
B21	
B22	

Ex	R
B23	
B24	
B25	
B26	
B27	
B28	
B29	
B30	

[0672] [表 137]

[0673]

Ex	R
B31	
B32	
B33	
B34	
B35	
B36	
B37	
B38	

Ex	R
B39	
B40	
B41	
B42	
B43	
B44	
B45	
B46	
B47	

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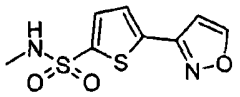
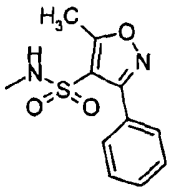
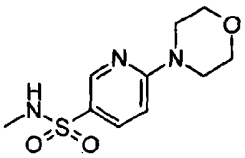
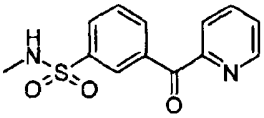
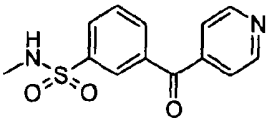
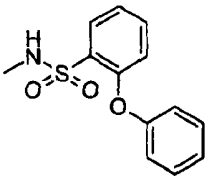
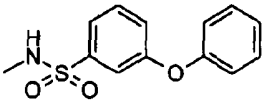
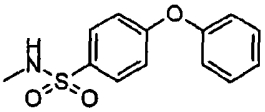
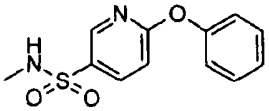
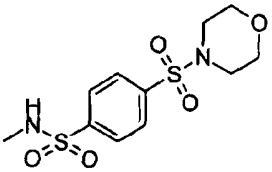
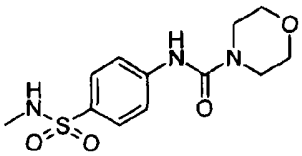
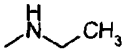
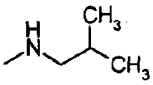
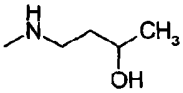
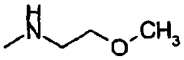
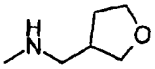
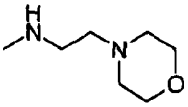
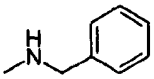
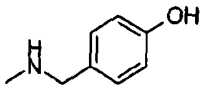
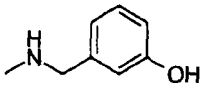
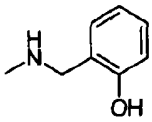
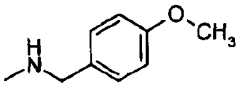
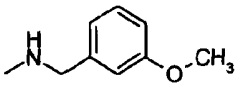
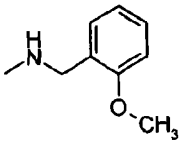
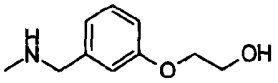
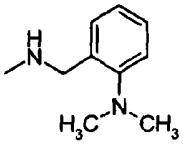
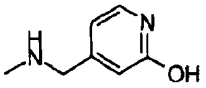
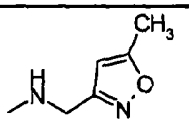
[0675]

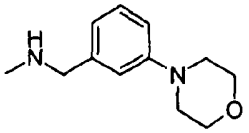
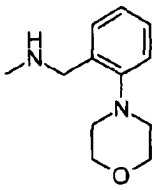
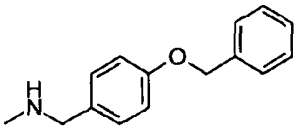
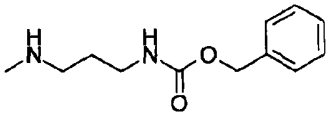
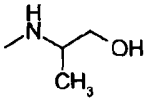
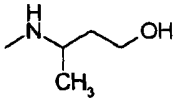
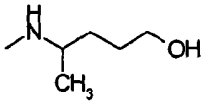
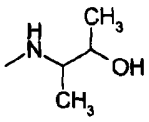
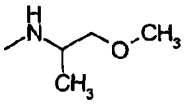
Ex	R
B48	
B49	
B50	
B51	
B52	
B53	
B54	
B55	

Ex	R
B56	
B57	
B58	
C1	
C2	
C3	
C4	
C5	
C6	
C7	

[0676] [表 139]

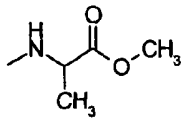
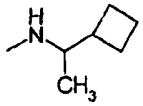
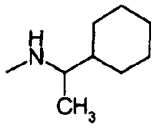
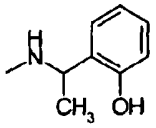
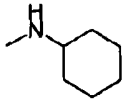
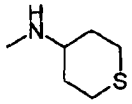
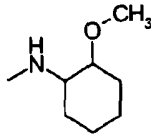
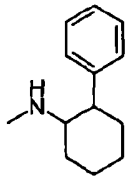
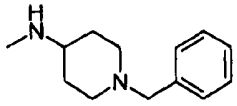
[0677]

Ex	R
C8	
C9	
C10	
C11	
C12	
C13	
C14	
C15	
C16	
C17	

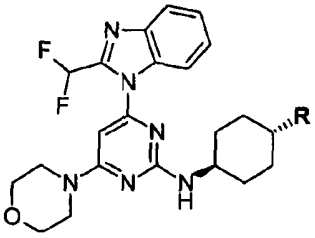
Ex	R
C18	
C19	
C20	
C21	
C22	
C23	
C24	
C25	
C26	

[0678] [表 140]

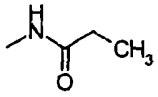
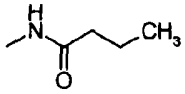
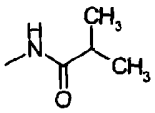
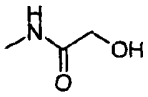
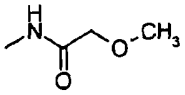
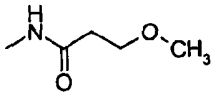
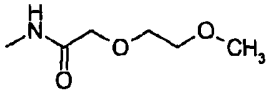
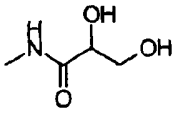
[0679]

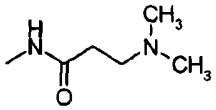
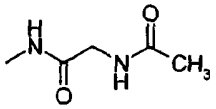
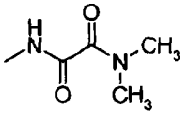
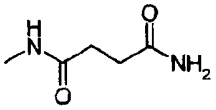
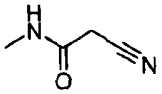
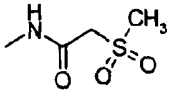
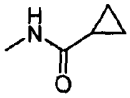
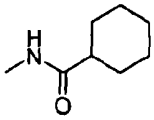
Ex	R
C27	
C28	
C29	
C30	
C31	
C32	
C33	
C34	
C35	

[0680] [表 141]



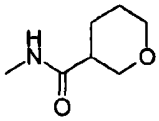
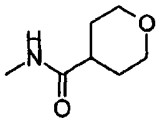
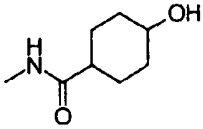
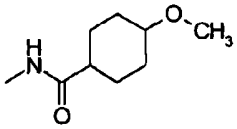
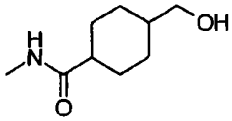
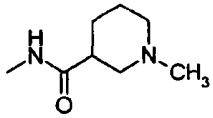
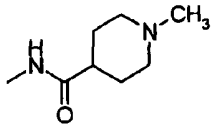
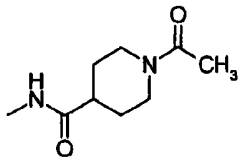
[0681]

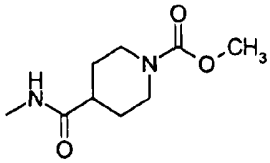
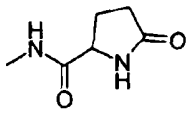
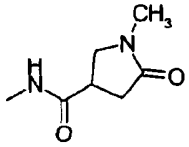
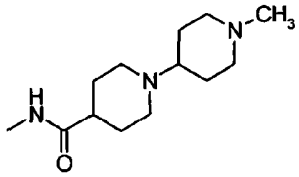
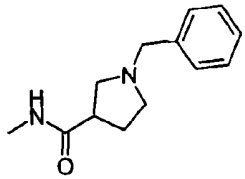
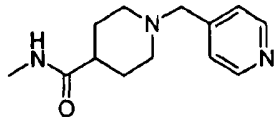
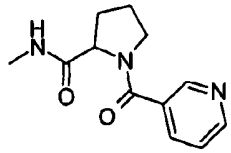
Ex	R
D1	
D2	
D3	
D4	
D5	
D6	
D7	
D8	

Ex	R
D9	
D10	
D11	
D12	
D13	
D14	
D15	
D16	

[0682] [表 142]

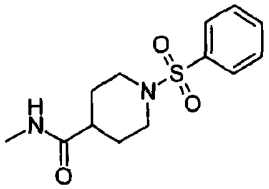
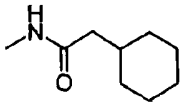
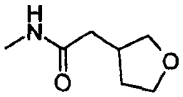
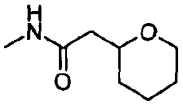
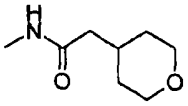
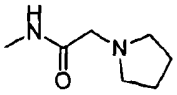
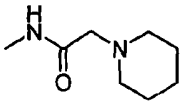
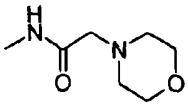
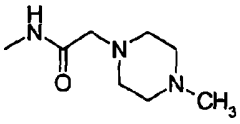
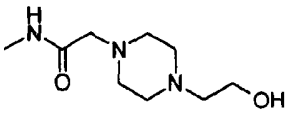
[0683]

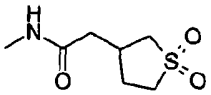
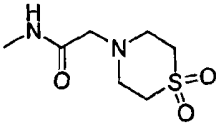
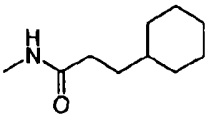
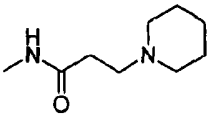
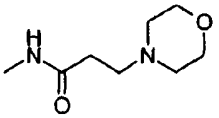
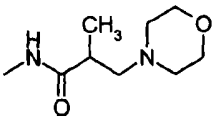
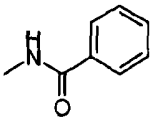
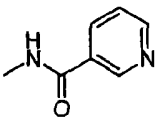
Ex	R
D17	
D18	
D19	
D20	
D21	
D22	
D23	
D24	

Ex	R
D25	
D26	
D27	
D28	
D29	
D30	
D31	

[0684] [表 143]

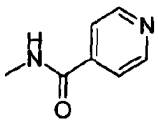
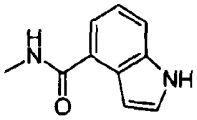
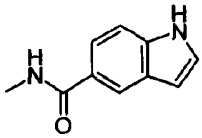
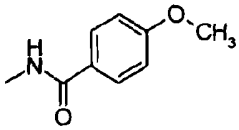
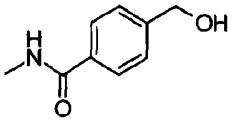
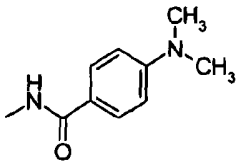
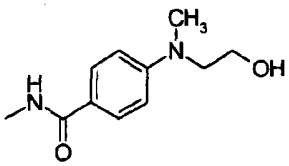
[0685]

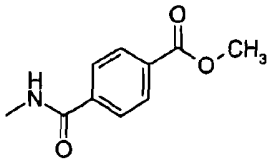
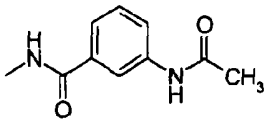
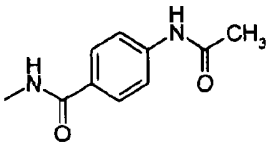
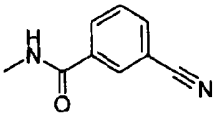
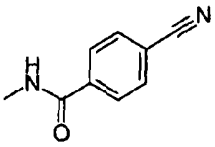
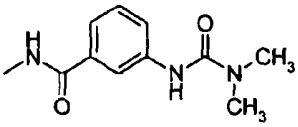
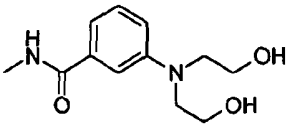
Ex	R
D32	
D33	
D34	
D35	
D36	
D37	
D38	
D39	
D40	
D41	

Ex	R
D42	
D43	
D44	
D45	
D46	
D47	
D48	
D49	

[0686] [表 144]

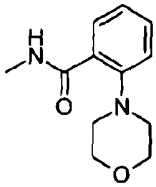
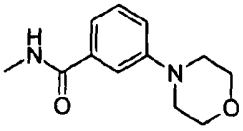
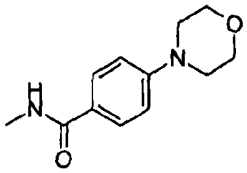
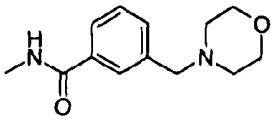
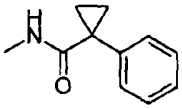
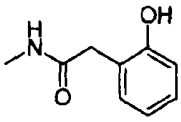
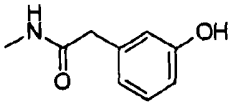
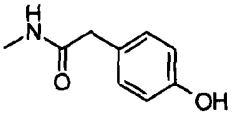
[0687]

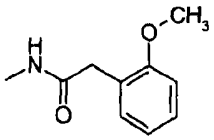
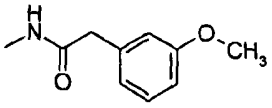
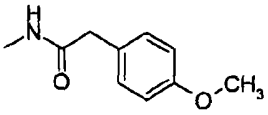
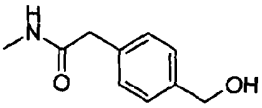
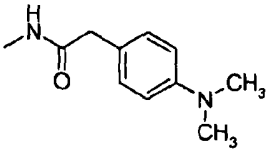
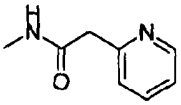
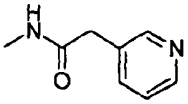
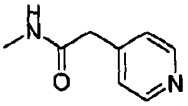
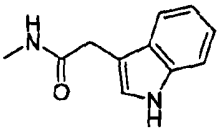
Ex	R
D50	
D51	
D52	
D53	
D54	
D55	
D56	

Ex	R
D57	
D58	
D59	
D60	
D61	
D62	
D63	

[0688] [表 145]

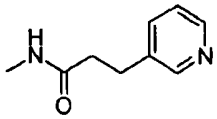
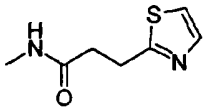
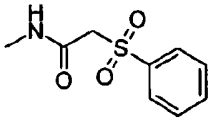
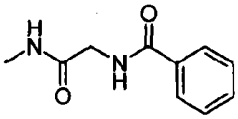
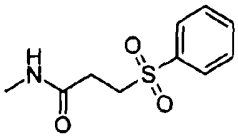
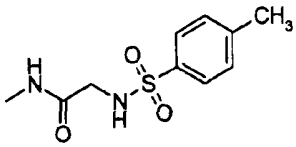
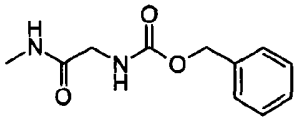
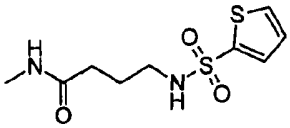
[0689]

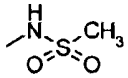
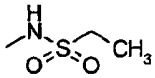
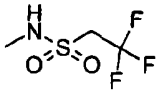
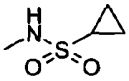
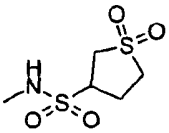
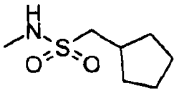
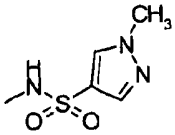
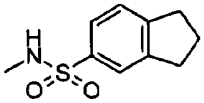
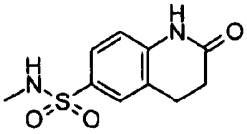
Ex	R
D64	
D65	
D66	
D67	
D68	
D69	
D70	
D71	

Ex	R
D72	
D73	
D74	
D75	
D76	
D77	
D78	
D79	
D80	

[0690] [表 146]

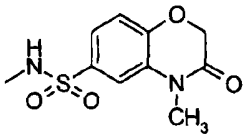
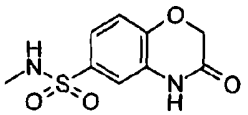
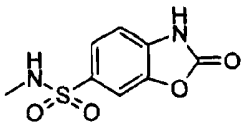
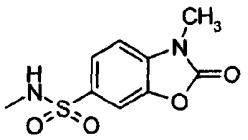
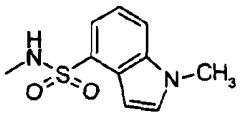
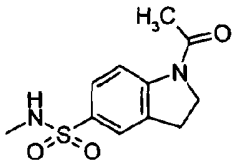
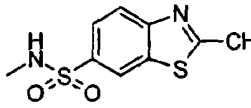
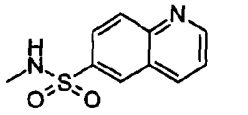
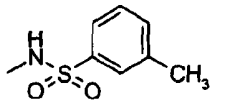
[0691]

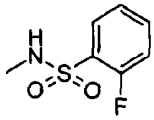
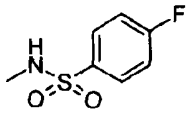
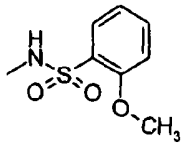
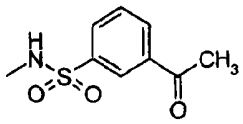
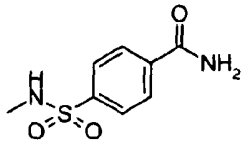
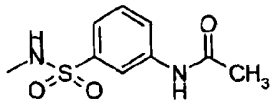
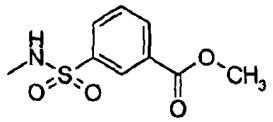
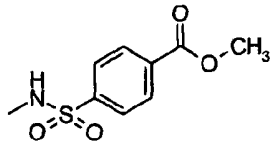
Ex	R
D81	
D82	
D83	
D84	
D85	
D86	
D87	
D88	

Ex	R
E1	
E2	
E3	
E4	
E5	
E6	
E7	
E8	
E9	

[0692] [表 147]

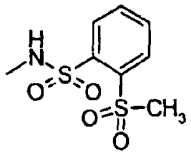
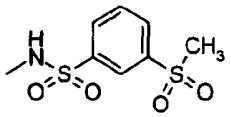
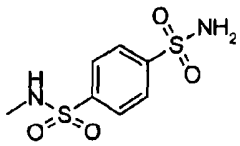
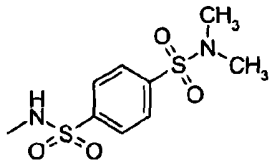
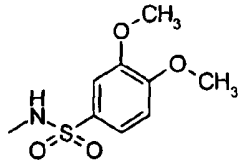
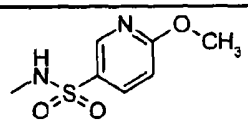
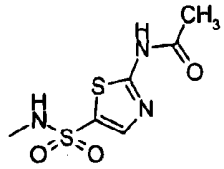
[0693]

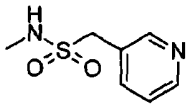
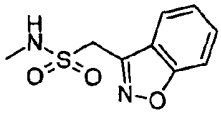
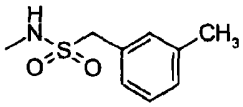
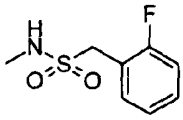
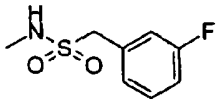
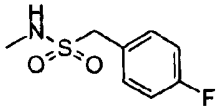
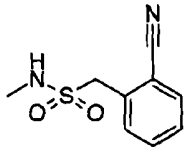
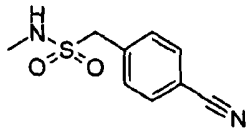
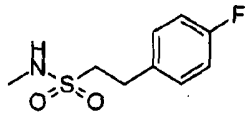
Ex	R
E10	
E11	
E12	
E13	
E14	
E15	
E16	
E17	
E18	

Ex	R
E19	
E20	
E21	
E22	
E23	
E24	
E25	
E26	

[0694] [表 148]

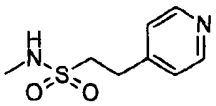
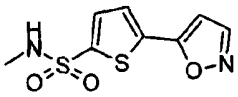
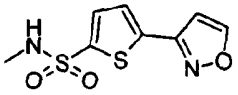
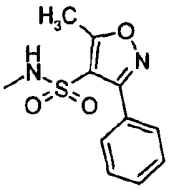
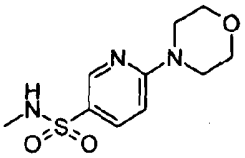
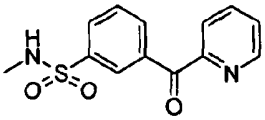
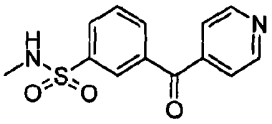
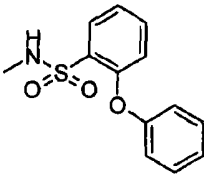
[0695]

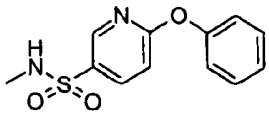
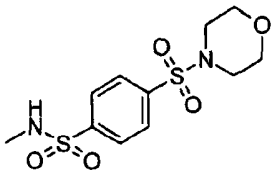
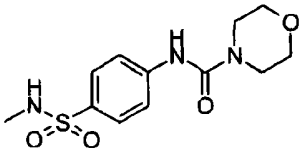
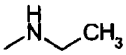
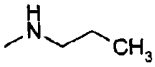
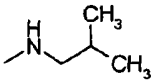
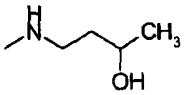
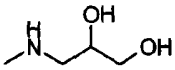
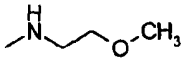
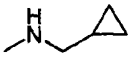
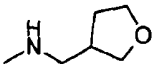
Ex	R
E27	
E28	
E29	
E30	
E31	
E32	
E33	

Ex	R
E34	
E35	
E36	
E37	
E38	
E39	
E40	
E41	
E42	

[0696] [表 149]

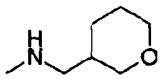
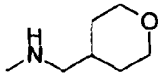
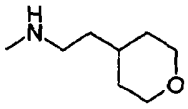
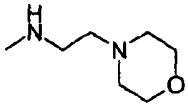
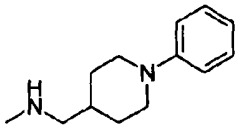
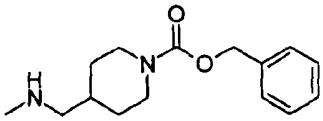
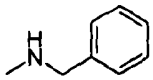
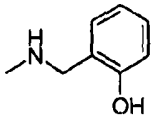
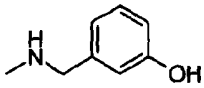
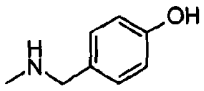
[0697]

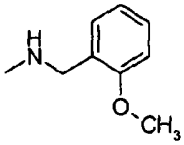
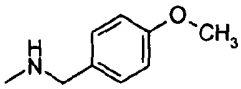
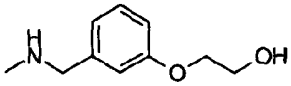
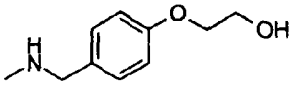
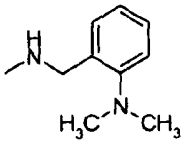
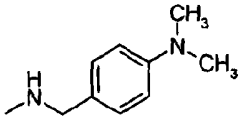
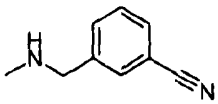
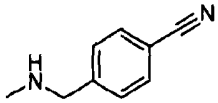
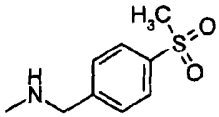
Ex	R
E43	
E44	
E45	
E46	
E47	
E48	
E49	
E50	

Ex	R
E51	
E52	
E53	
F1	
F2	
F3	
F4	
F5	
F6	
F7	
F8	

[0698] [表 150]

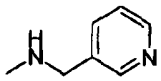
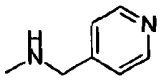
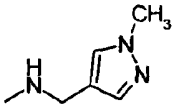
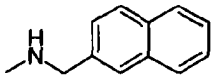
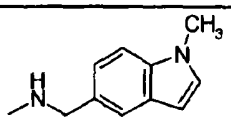
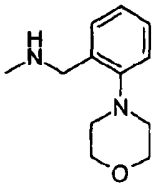
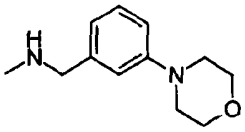
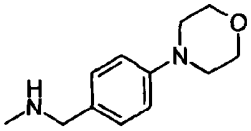
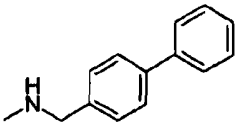
[0699]

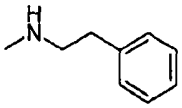
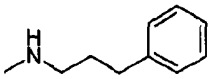
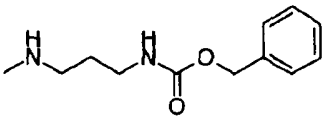
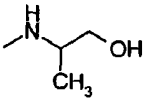
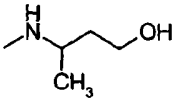
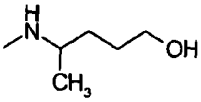
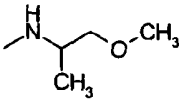
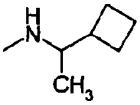
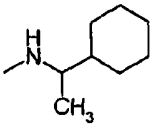
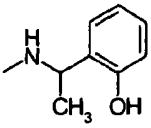
Ex	R
F9	
F10	
F11	
F12	
F13	
F14	
F15	
F16	
F17	
F18	

Ex	R
F19	
F20	
F21	
F22	
F23	
F24	
F25	
F26	
F27	

[0700] [表 151]

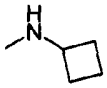
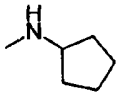
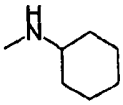
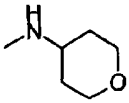
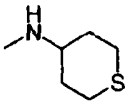
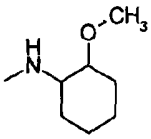
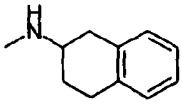
[0701]

Ex	R
F28	
F29	
F30	
F31	
F32	
F33	
F34	
F35	
F36	

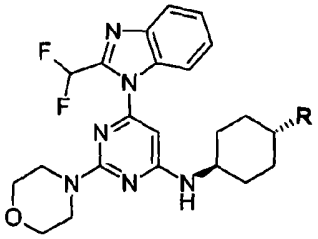
Ex	R
F37	
F38	
F39	
F40	
F41	
F42	
F43	
F44	
F45	
F46	

[0702] [表 152]

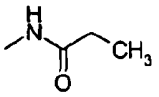
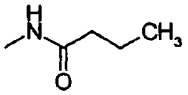
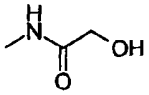
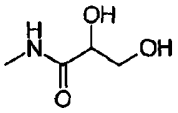
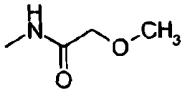
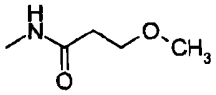
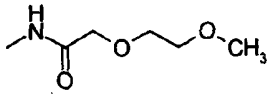
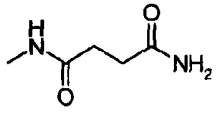
[0703]

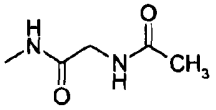
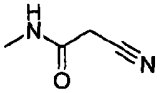
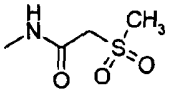
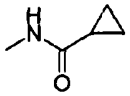
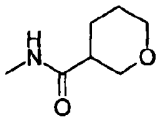
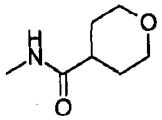
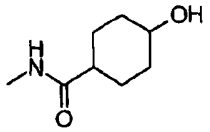
Ex	R
F47	
F48	
F49	
F50	
F51	
F52	
F53	

[0704] [表 153]



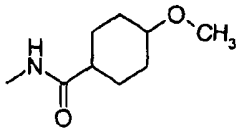
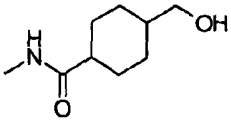
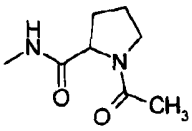
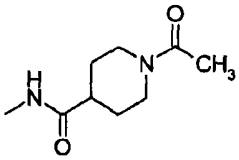
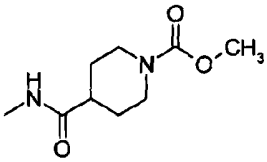
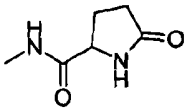
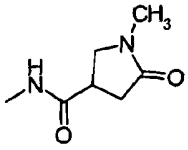
[0705]

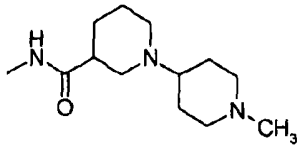
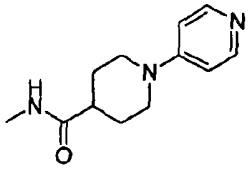
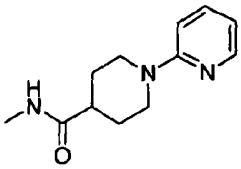
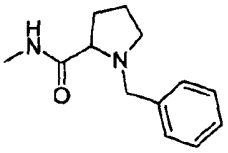
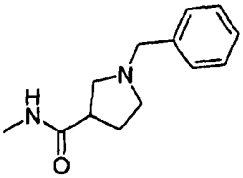
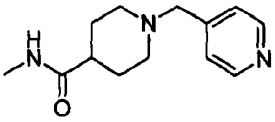
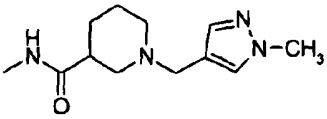
Ex	R
G1	
G2	
G3	
G4	
G5	
G6	
G7	
G8	

Ex	R
G9	
G10	
G11	
G12	
G13	
G14	
G15	

[0706] [表 154]

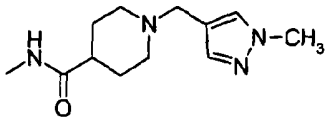
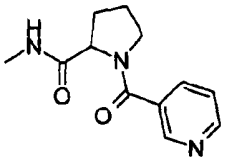
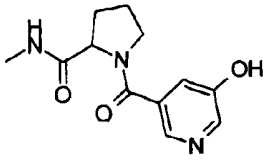
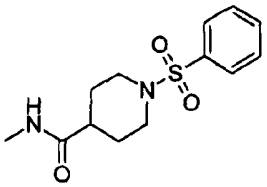
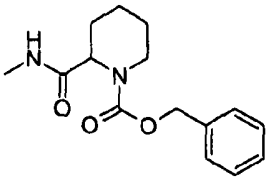
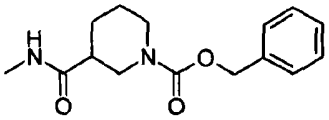
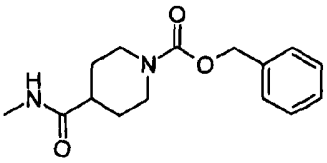
[0707]

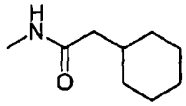
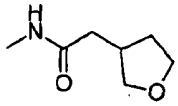
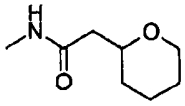
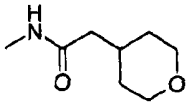
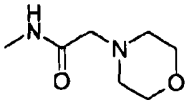
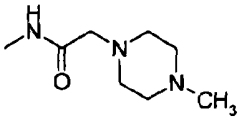
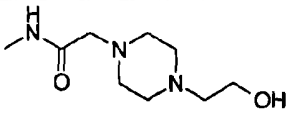
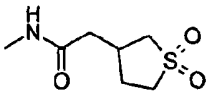
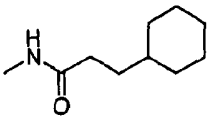
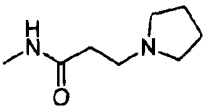
Ex	R
G16	
G17	
G18	
G19	
G20	
G21	
G22	

Ex	R
G23	
G24	
G25	
G26	
G27	
G28	
G29	

[0708] [表 155]

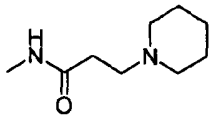
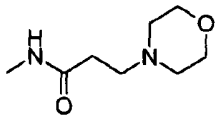
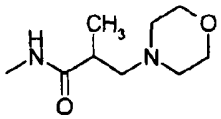
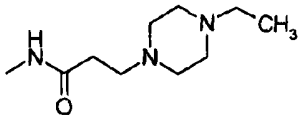
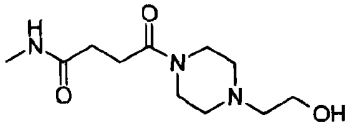
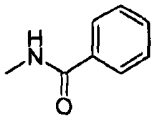
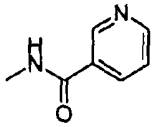
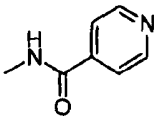
[0709]

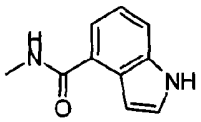
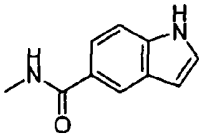
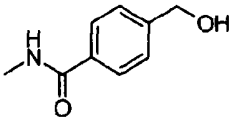
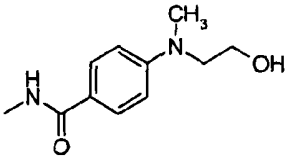
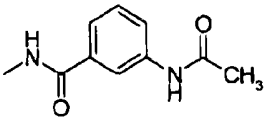
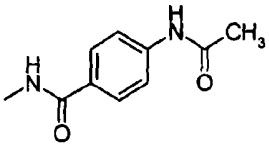
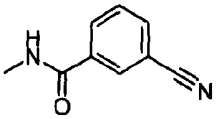
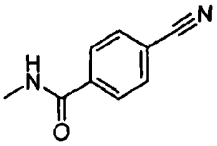
Ex	R
G30	
G31	
G32	
G33	
G34	
G35	
G36	

Ex	R
G37	
G38	
G39	
G40	
G41	
G42	
G43	
G44	
G45	
G46	

[0710] [表 156]

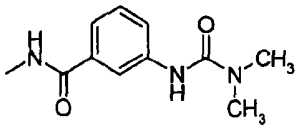
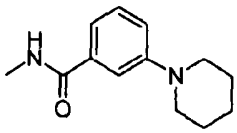
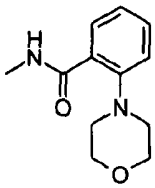
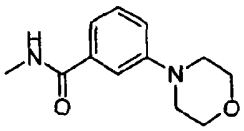
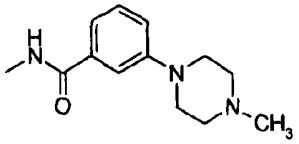
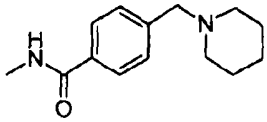
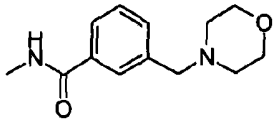
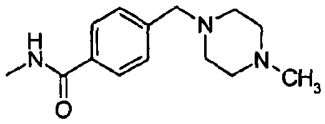
[0711]

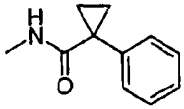
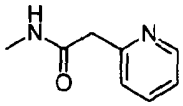
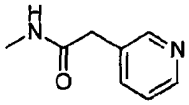
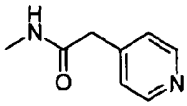
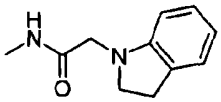
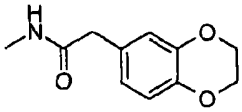
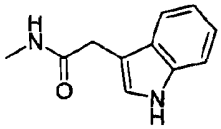
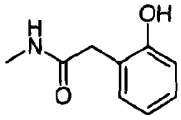
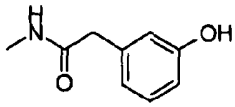
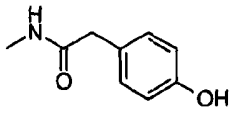
Ex	R
G47	
G48	
G49	
G50	
G51	
G52	
G53	
G54	

Ex	R
G55	
G56	
G57	
G58	
G59	
G60	
G61	
G62	

[0712] [表 157]

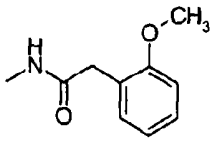
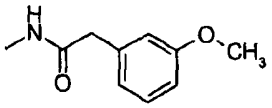
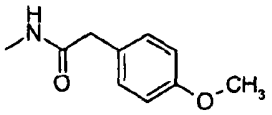
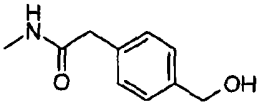
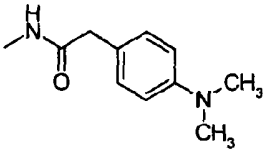
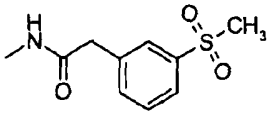
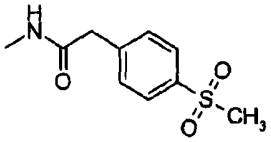
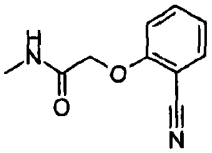
[0713]

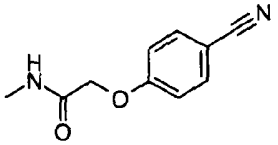
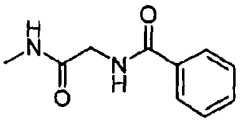
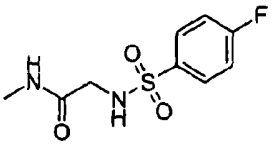
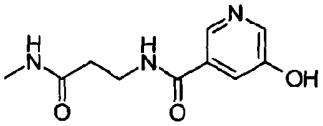
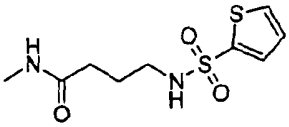
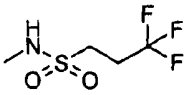
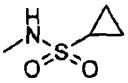
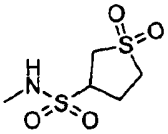
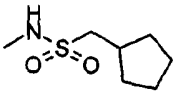
Ex	R
G63	
G64	
G65	
G66	
G67	
G68	
G69	
G70	

Ex	R
G71	
G72	
G73	
G74	
G75	
G76	
G77	
G78	
G79	
G80	

[0714] [表 158]

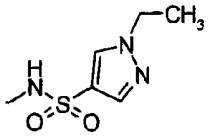
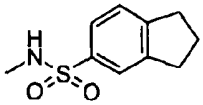
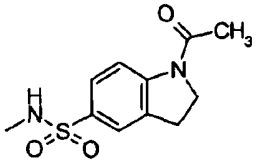
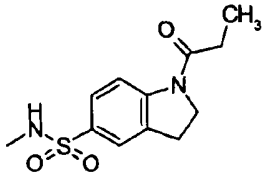
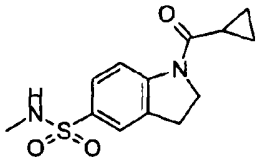
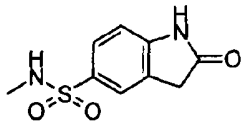
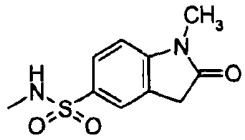
[0715]

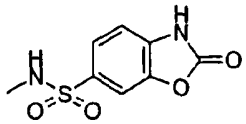
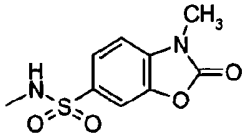
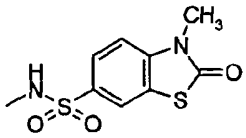
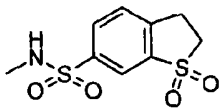
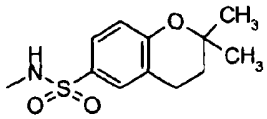
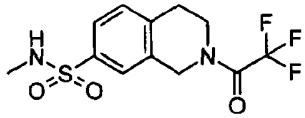
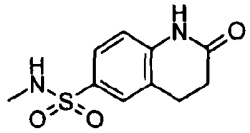
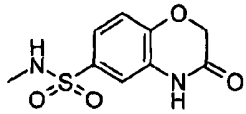
Ex	R
G81	
G82	
G83	
G84	
G85	
G86	
G87	
G88	

Ex	R
G89	
G90	
G91	
G92	
G93	
H1	
H2	
H3	
H4	

[0716] [表 159]

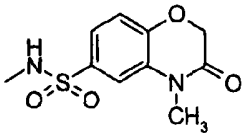
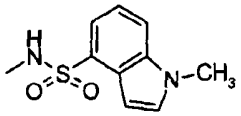
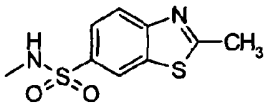
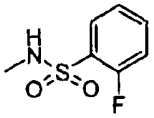
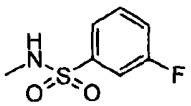
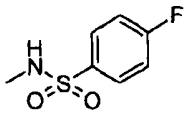
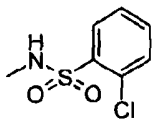
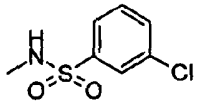
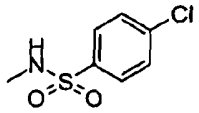
[0717]

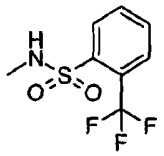
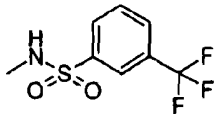
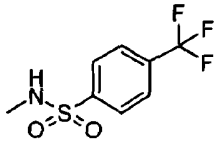
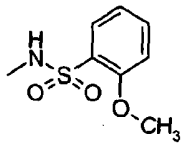
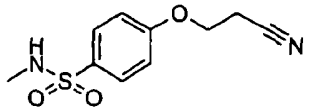
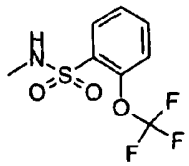
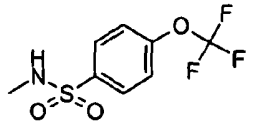
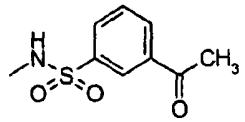
Ex	R
H5	
H6	
H7	
H8	
H9	
H10	
H11	

Ex	R
H12	
H13	
H14	
H15	
H16	
H17	
H18	
H19	

[0718] [表 160]

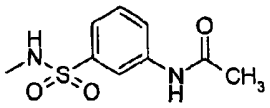
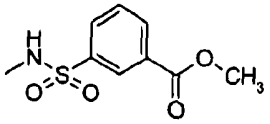
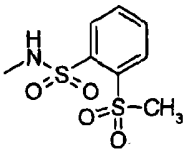
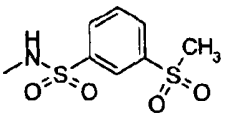
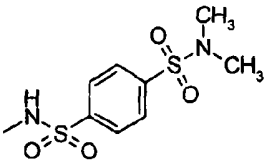
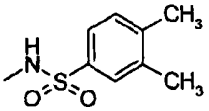
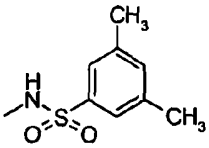
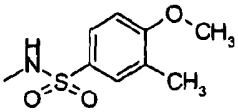
[0719]

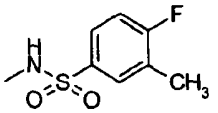
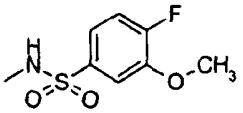
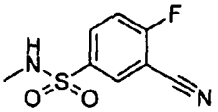
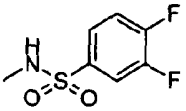
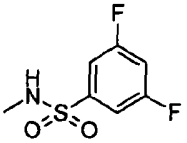
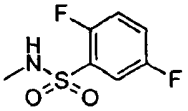
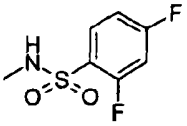
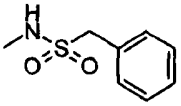
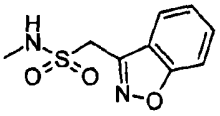
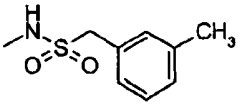
Ex	R
H20	
H21	
H22	
H23	
H24	
H25	
H26	
H27	
H28	

Ex	R
H29	
H30	
H31	
H32	
H33	
H34	
H35	
H36	

[0720] [表 161]

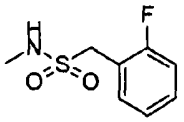
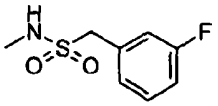
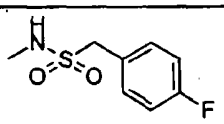
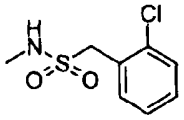
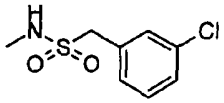
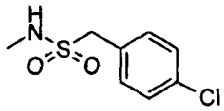
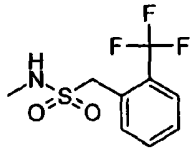
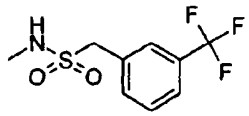
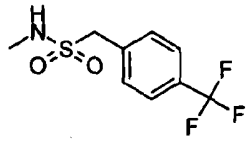
[0721]

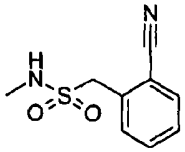
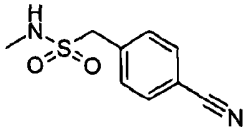
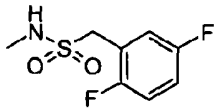
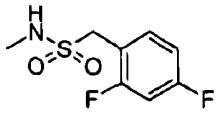
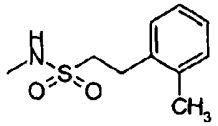
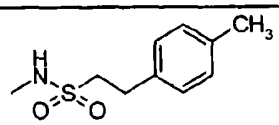
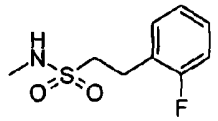
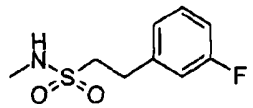
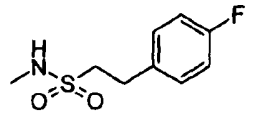
Ex	R
H37	
H38	
H39	
H40	
H41	
H42	
H43	
H44	

Ex	R
H45	
H46	
H47	
H48	
H49	
H50	
H51	
H52	
H53	
H54	

[0722] [表 162]

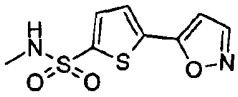
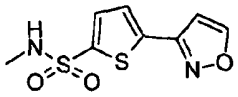
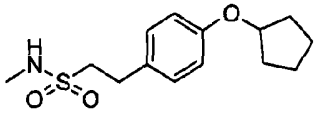
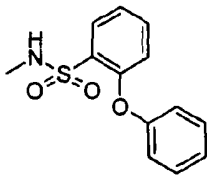
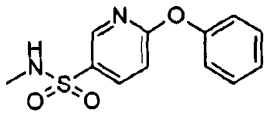
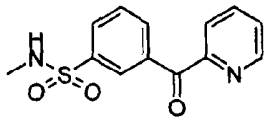
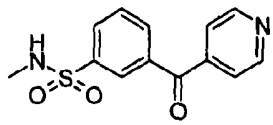
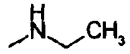
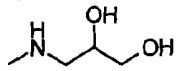
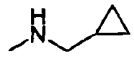
[0723]

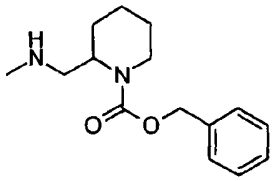
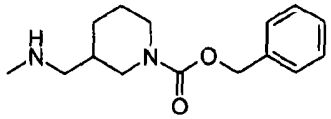
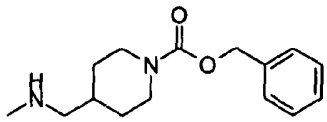
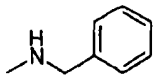
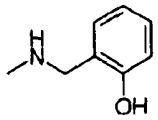
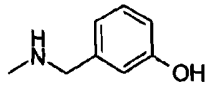
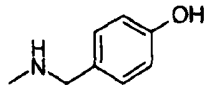
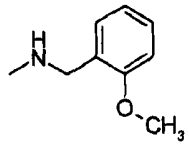
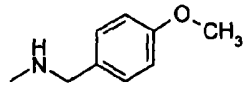
Ex	R
H55	
H56	
H57	
H58	
H59	
H60	
H61	
H62	
H63	

Ex	R
H64	
H65	
H66	
H67	
H68	
H69	
H70	
H71	
H72	

[0724] [表 163]

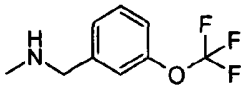
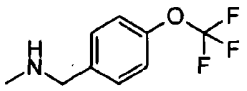
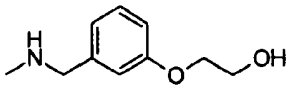
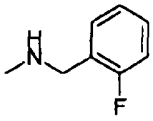
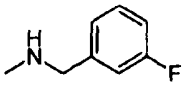
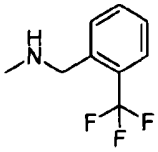
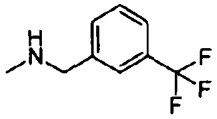
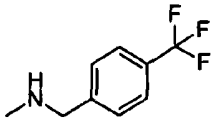
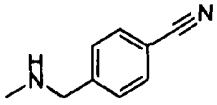
[0725]

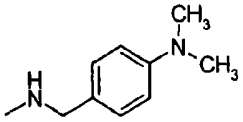
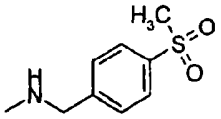
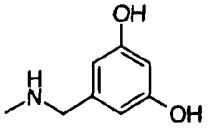
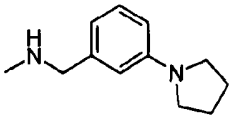
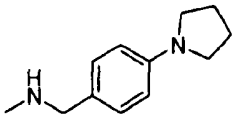
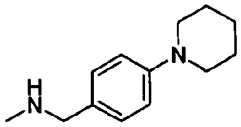
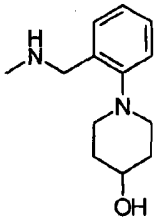
Ex	R
H73	
H74	
H75	
H76	
H77	
H78	
H79	
J1	
J2	
J3	

Ex	R
J4	
J5	
J6	
J7	
J8	
J9	
J10	
J11	
J12	

[0726] [表 164]

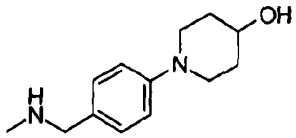
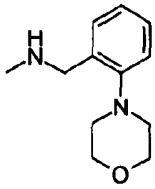
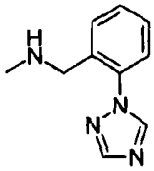
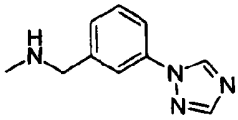
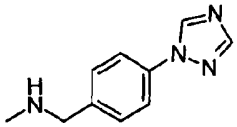
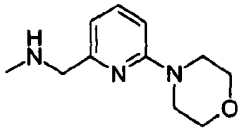
[0727]

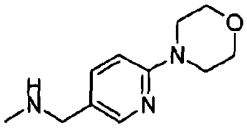
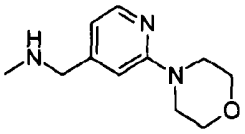
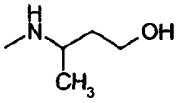
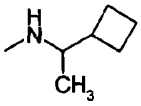
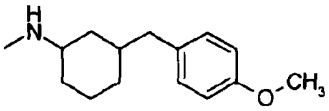
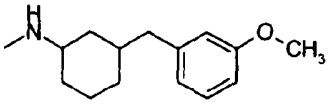
Ex	R
J13	
J14	
J15	
J16	
J17	
J18	
J19	
J20	
J21	

Ex	R
J22	
J23	
J24	
J25	
J26	
J27	
J28	

[0728] [表 165]

[0729]

Ex	R
J29	
J30	
J31	
J32	
J33	
J34	

Ex	R
J35	
J36	
J37	
J38	
J39	
J40	

[0730] [表 166]

[0731]

Ex	ESI+	RT	Ex	ESI+	RT	Ex	ESI+	RT
A1	501	3.01	A33	570	2.58	A65	652	3.03
A2	515	3.16	A34	572	2.49	A66	684	3.37
A3	515	3.14	A35	585	2.5	A67	634	3.35
A4	503	2.81	A36	615	2.5	A68	634	3.26
A5	517	2.99	A37	620	2.79	A69	648	2.68
A6	531	2.96	A38	583	3.71	A70	616	3.58
A7	561	3.07	A39	584	2.59	A71	564	2.62
A8	533	2.73	A40	586	2.51	A72	564	2.57
A9	519	3.06	A41	549	3.26	A73	564	2.56
A10	512	2.85	A42	550	3.27	A74	579	3.06
A11	530	2.49	A43	550	2.9	A75	579	3
A12	544	2.75	A44	550	2.86	A76	593	3.32
A13	544	2.85	A45	588	3.17	A77	593	3.28
A14	544	2.76	A46	588	3.2	A78	593	3.26
A15	565	2.79	A47	565	3.4	A79	593	3
A16	513	3.06	A48	565	3.1	A80	606	2.7
A17	557	3.08	A49	565	3.07	A81	578	2.57
A18	557	3.01	A50	579	3.36	A82	584	3.04
A19	571	3.01	A51	579	3.3	A83	627	3.07
A20	585	3.21	A52	579	3.28	A84	606	3.1
A21	585	3.1	A53	579	3.05	A85	656	3.21
A22	556	2.78	A54	593	3.27	A86	636	3.27
A23	570	2.84	A55	592	2.9	A87	676	3.09
A24	570	2.58	A56	592	3.11	B1	537	2.88
A25	570	2.54	A57	592	3.31	B2	551	2.97
A26	598	2.92	A58	622	3.14	B3	591	2.95
A27	614	3.13	A59	607	3.32	B4	549	2.89
A28	632	2.81	A60	606	3.11	B5	627	2.78
A29	569	3.57	A61	606	3.08	B6	591	3.18
A30	557	3	A62	574	3.23	B7	605	3.26
A31	571	3.24	A63	574	3.22	B8	585	3.01
A32	571	3.05	A64	635	3.13	B9	589	2.8

[0732] [表 167]

[0733]

Ex	ESI+	RT
B10	576	2.74
B11	643	2.99
B12	654	2.83
B13	670	2.98
B14	656	2.92
B15	642	2.86
B16	656	2.9
B17	636	2.96
B18	638	3
B19	638	3
B20	668	2.9
B21	615	3
B22	627	2.97
B23	628	2.79
B24	642	2.87
B25	643	3.05
B26	643	3.06
B27	663	3.06
B28	663	2.85
B29	664	2.78
B30	685	2.9
B31	699	2.99
B32	692	2.95
B33	656	2.82
B34	645	2.95
B35	616	3.05
B36	649	2.88
B37	599	3.07
B38	600	2.77
B39	640	3.07
B40	624	2.97
B41	624	2.94

Ex	ESI+	RT
B42	613	3.15
B43	614	2.55
B44	629	3.13
B45	673	3.13
B46	661	3.26
B47	661	3.25
B48	658	2.88
B49	666	3.2
B50	671	2.96
B51	690	3.06
B52	690	3
B53	677	3.24
B54	677	3.26
B55	677	3.26
B56	678	3.17
B57	734	2.97
B58	713	2.86
C1	473	2.26
C2	501	2.4
C3	517	2.24
C4	503	2.29
C5	529	2.26
C6	558	2.33
C7	535	2.43
C8	551	2.33
C9	551	2.34
C10	551	2.35
C11	565	2.47
C12	565	2.45
C13	565	2.45
C14	595	2.34
C15	578	2.53

Ex	ESI+	RT
C16	552	2.18
C17	540	2.23
C18	620	2.45
C19	620	2.46
C20	641	2.69
C21	636	2.58
C22	503	2.21
C23	517	2.23
C24	531	2.26
C25	517	2.25
C26	517	2.3
C27	531	2.28
C28	527	2.48
C29	555	2.64
C30	565	2.48
C31	527	2.48
C32	545	2.35
C33	557	2.44
C34	603	2.7
C35	618	1.93
D1	500	2.69
D2	514	2.8
D3	514	2.78
D4	502	2.5
D5	516	2.68
D6	530	2.64
D7	560	2.74
D8	532	2.43
D9	543	2.09
D10	543	2.46
D11	543	2.55
D12	543	2.46

[0734] [表 168]

[0735]

Ex	ESI+	RT	Ex	ESI+	RT	Ex	ESI+	RT
D13	511	2.53	D45	583	2.17	D77	563	2.45
D14	564	2.48	D46	585	2.1	D78	563	2.32
D15	512	2.73	D47	599	2.19	D79	563	2.26
D16	554	3.03	D48	548	2.89	D80	601	2.85
D17	556	2.75	D49	549	2.68	D81	577	2.3
D18	556	2.68	D50	549	2.67	D82	583	2.73
D19	570	2.68	D51	587	2.8	D83	626	2.7
D20	584	2.87	D52	587	2.82	D84	605	2.74
D21	584	2.74	D53	578	2.92	D85	640	2.74
D22	569	2.15	D54	578	2.7	D86	655	2.82
D23	569	2.13	D55	591	2.97	D87	635	2.86
D24	597	2.6	D56	621	2.8	D88	675	2.71
D25	613	2.77	D57	606	2.95	E1	522	2.53
D26	555	2.48	D58	605	2.76	E2	536	2.62
D27	569	2.53	D59	605	2.74	E3	590	2.72
D28	652	1.8	D60	573	2.86	E4	548	2.64
D29	631	2.36	D61	573	2.85	E5	626	2.52
D30	646	2.15	D62	634	2.78	E6	590	2.98
D31	646	2.59	D63	651	2.71	E7	588	2.54
D32	695	2.87	D64	633	3	E8	624	3
D33	568	3.11	D65	633	2.92	E9	653	2.59
D34	556	2.68	D66	633	2.9	E10	669	2.76
D35	570	2.87	D67	647	2.29	E11	655	2.69
D36	570	2.72	D68	588	3.15	E12	641	2.62
D37	555	2.13	D69	578	2.83	E13	655	2.67
D38	569	2.18	D70	578	2.69	E14	637	2.79
D39	571	2.15	D71	578	2.65	E15	667	2.66
D40	584	2.1	D72	592	2.93	E16	655	2.83
D41	614	2.1	D73	592	2.89	E17	635	2.73
D42	604	2.53	D74	592	2.88	E18	598	2.88
D43	619	2.5	D75	592	2.66	E19	602	2.79
D44	582	3.21	D76	605	2.58	E20	602	2.84

[0736] [表 169]

[0737]

Ex	ESI+	RT
E21	614	2.78
E22	626	2.74
E23	627	2.54
E24	641	2.64
E25	642	2.84
E26	642	2.85
E27	662	2.84
E28	662	2.62
E29	663	2.54
E30	691	2.73
E31	644	2.72
E32	615	2.82
E33	648	2.64
E34	599	2.51
E35	639	2.85
E36	612	2.95
E37	616	2.86
E38	616	2.86
E39	616	2.86
E40	623	2.75
E41	623	2.72
E42	630	2.94
E43	613	2.28
E44	657	2.66
E45	657	2.66
E46	665	3
E47	670	2.72
E48	689	2.84
E49	689	2.79
E50	676	3.06
E51	677	2.98
E52	733	2.75

Ex	ESI+	RT
E53	712	2.63
F1	472	2.24
F2	486	2.34
F3	500	2.42
F4	516	2.22
F5	518	2.15
F6	502	2.27
F7	498	2.34
F8	528	2.26
F9	542	2.35
F10	542	2.29
F11	556	2.35
F12	557	2.39
F13	617	2.5
F14	675	2.77
F15	534	2.47
F16	550	2.46
F17	550	2.38
F18	550	2.38
F19	564	2.58
F20	564	2.51
F21	594	2.39
F22	594	2.37
F23	577	2.64
F24	577	2.64
F25	559	2.38
F26	559	2.35
F27	612	2.27
F28	535	2.21
F29	535	2.21
F30	538	2.24
F31	584	2.7

Ex	ESI+	RT
F32	587	2.65
F33	619	2.53
F34	619	2.51
F35	619	2.51
F36	610	2.85
F37	548	2.62
F38	562	2.7
F39	635	2.71
F40	502	2.2
F41	516	2.2
F42	530	2.27
F43	516	2.34
F44	526	2.28
F45	554	2.42
F46	564	2.24
F47	498	2.15
F48	512	2.19
F49	526	2.26
F50	528	2.02
F51	544	2.12
F52	556	2.24
F53	574	2.42
G1	500	2.82
G2	514	2.93
G3	502	2.65
G4	532	2.58
G5	516	2.82
G6	530	2.78
G7	560	2.87
G8	543	2.6
G9	543	2.61
G10	511	2.67

[0738] [表 170]

[0739]

Ex	ESI+	RT	Ex	ESI+	RT	Ex	ESI+	RT
G11	564	2.62	G43	614	2.25	G75	603	3.18
G12	512	2.86	G44	604	2.66	G76	620	2.96
G13	556	2.89	G45	582	3.31	G77	601	2.97
G14	556	2.82	G46	569	2.29	G78	578	2.95
G15	570	2.81	G47	583	2.31	G79	578	2.82
G16	584	2.99	G48	585	2.26	G80	578	2.78
G17	584	2.87	G49	599	2.32	G81	592	3.04
G18	583	2.74	G50	612	2.27	G82	592	3
G19	597	2.73	G51	656	2.29	G83	592	2.99
G20	613	2.89	G52	548	3.01	G84	592	2.78
G21	555	2.62	G53	549	2.82	G85	605	2.76
G22	569	2.67	G54	549	2.81	G86	640	2.75
G23	652	1.99	G55	587	2.92	G87	640	2.73
G24	632	2.38	G56	587	2.94	G88	603	3.01
G25	632	2.42	G57	578	2.83	G89	603	2.94
G26	631	2.51	G58	621	2.92	G90	605	2.86
G27	631	2.48	G59	605	2.88	G91	659	2.89
G28	646	2.28	G60	605	2.87	G92	636	2.68
G29	649	2.32	G61	573	2.98	G93	675	2.83
G30	649	2.3	G62	573	2.97	H1	604	2.82
G31	646	2.72	G63	634	2.91	H2	548	2.62
G32	662	2.69	G64	631	3.09	H3	626	2.52
G33	695	2.97	G65	633	3.1	H4	590	2.99
G34	689	3.23	G66	633	3.03	H5	602	2.6
G35	689	3.18	G67	646	2.46	H6	624	3.02
G36	689	3.13	G68	645	2.44	H7	667	2.65
G37	568	3.21	G69	647	2.42	H8	681	2.76
G38	556	2.81	G70	660	2.46	H9	693	2.79
G39	570	2.99	G71	588	3.26	H10	639	2.53
G40	570	2.85	G72	563	2.63	H11	653	2.61
G41	571	2.3	G73	563	2.5	H12	641	2.62
G42	584	2.25	G74	563	2.41	H13	655	2.66

[0740] [表 171]

[0741]

Ex	ESI+	RT
H14	671	2.77
H15	674	2.58
H16	668	3.05
H17	735	2.85
H18	653	2.58
H19	655	2.68
H20	669	2.75
H21	637	2.78
H22	655	2.82
H23	602	2.79
H24	602	2.79
H25	602	2.85
H26	618	2.88
H27	618	2.97
H28	618	2.98
H29	652	2.9
H30	652	3
H31	652	3.02
H32	614	2.78
H33	653	2.62
H34	668	2.96
H35	668	3.04
H36	626	2.74
H37	641	2.64
H38	642	2.85
H39	662	2.88
H40	662	2.61
H41	691	2.73
H42	612	2.97
H43	612	3
H44	628	2.92
H45	616	2.97

Ex	ESI+	RT
H46	632	2.88
H47	627	2.83
H48	620	2.94
H49	620	2.97
H50	620	2.87
H51	620	2.86
H52	598	2.86
H53	639	2.87
H54	612	2.96
H55	616	2.88
H56	616	2.87
H57	616	2.87
H58	632	2.96
H59	632	2.97
H60	632	2.98
H61	666	3
H62	666	2.99
H63	666	3
H64	623	2.74
H65	623	2.71
H66	634	2.88
H67	634	2.91
H68	626	3.08
H69	626	3.09
H70	630	2.99
H71	630	2.98
H72	630	2.96
H73	657	2.66
H74	657	2.66
H75	668	3.16
H76	676	3.09
H77	677	3

Ex	ESI+	RT
H78	689	2.86
H79	689	2.79
J1	472	2.32
J2	518	2.25
J3	498	2.41
J4	675	2.77
J5	675	2.74
J6	675	2.74
J7	534	2.51
J8	550	2.5
J9	550	2.43
J10	550	2.41
J11	564	2.58
J12	564	2.58
J13	618	2.7
J14	618	2.66
J15	594	2.43
J16	552	2.51
J17	552	2.54
J18	602	2.67
J19	602	2.66
J20	602	2.64
J21	559	2.41
J22	577	2.61
J23	612	2.33
J24	566	2.35
J25	603	2.74
J26	603	2.78
J27	617	2.82
J28	633	2.49
J29	633	2.51
J30	619	2.56

[0742] [表 172]

[0743]

Ex	ESI+	RT
J31	601	2.38
J32	601	2.4

J33	601	2.4
J34	620	2.54
J35	620	2.41
J36	620	2.41
J37	516	2.31
J38	526	2.57
J39	646	2.86
J40	646	2.84

[0744] 工业适用性

[0745] 作为本发明药物的有效成分的化合物具有PI3Kδ选择性抑制作用和/或IL-2产生抑制作用和/或B细胞增殖抑制作用（包括活化抑制作用）以及基于这些的良好的药理作用，因此，本发明的药物组合物可用作各种脏器移植中的排斥反应、变应性疾病（哮喘、特应性皮炎等）、自身免疫疾病（类风湿性关节炎、牛皮癣、溃疡性结肠炎、克罗恩病、全身性红斑狼疮等）和血液肿瘤（白血病等）等的预防或治疗剂。