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(71)申请人 英安塔制药有限公司
地址 美国马萨诸塞州

(72)发明人 约瑟夫·帕纳雷塞
德克斯特·戴维斯
塞缪尔·巴特利特 凯瑟琳·崇
纳撒尼尔·肯顿 柯日新

(74)专利代理机构 成都超凡明远知识产权代理有限公司 51258
代理人 王晖 刘书芝

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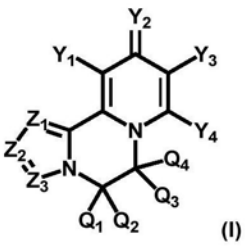
(54)发明名称

官能化杂环化合物作为抗病毒剂

(57)摘要

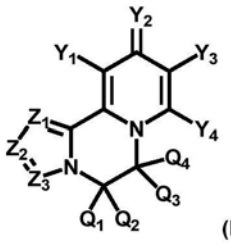
本发明公开了式(I)的化合物，或其药学上可接受的盐，其抑制由乙型肝炎病毒(HBV)编码的一种或多种蛋白质或干扰乙型肝炎病毒的HBV生命周期的功能，并且还可用作抗病毒剂。本发明进一步涉及用于向患有HBV感染的受试者给药的包括上述化合物的药物组合物。本发明还涉及通过给药包括本发明的化合物的药物组合物来治疗受试者中的HBV感染的方法。



(I)

CN 113271946 A

1.一种由式(I)表示的化合物：



(I)，

或其药学上可接受的盐、N-氧化物、酯和前药，其中：

Q_1、Q_2、Q_3和Q_4各自独立地选自氢、卤素、$NR_{11}R_{12}$、任选取代的-C_1-C_6烷基、任选取代的-C_1-C_6烷氧基、任选取代的-C_3-C_8环烷基；任选取代的-C_3-C_8环烯基；任选取代的3-至8-元杂环烷基；任选取代的芳基；以及任选取代的杂芳基；

替代地，Q_1和Q_2中的一个和Q_3和Q_4中的一个与它们所连接的碳原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环或碳环；

替代地，Q_1和Q_2与它们所连接的碳原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环或碳环；

替代地，Q_3和Q_4与它们所连接的碳原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环或碳环；

Y_1是氢、卤素或任选取代的C_1-C_6烷基；

Y_2是O、NR_{11}、N(OR_{11})或N(NR_{11})；

Y_3是-$COOR_{11}$、-C(O)$NHSO_2R_{11}$、-C(O)$NHSO_2NR_{11}R_{12}$或1,2,4-噁二唑-3-基-5(4H)-酮，或Y_3是任选取代的芳基、任选取代的杂芳基、任选取代的-C_5-C_6环烷基或任选取代的5-至6-元杂环烷基；

Y_4是氢或任选取代的甲基；

替代地，Y_2和Y_3一起形成包含1、2或3个双键的任选取代的5-12元杂环；

Z_1是N或CR_1，Z_2是N或CR_2，并且Z_3是N或CR_3，前提是Z1、Z_2和Z_3中的至少一个是N；前提是当Z_3是N，Z_1是CR_1并且Z_2是CR_2时，R_2不是氢；卤素；氰基；任选取代的-C_1-C_6烷基；任选取代的-C_3-C_7环烷基；任选取代的3-至7-元杂环烷基；-NH_2；-NHC_1-C_6烷基；-OH；或-OC_1-C_6烷基；

R_1、R_2和R_3各自独立地选自：

1)氢；

2)卤素；

3)-NO_2；

4)氰基；

5)任选取代的-C_1-C_8烷基；

6)任选取代的-C_2-C_8烯基；

7)任选取代的-C_2-C_8炔基；

8)任选取代的-C_3-C_8环烷基；

9)任选取代的3-至12-元杂环烷基；

10)任选取代的芳基；

11)任选取代的芳基烷基；

12)任选取代的杂芳基；

13)任选取代的杂芳基烷基；

14)-SR_{11}；

15)-$S(O)_2R_{11}$；

16)-$S(O)_2N(R_{11})(R_{12})$；

17)-$C(O)R_{11}$；

18)-$C(O)OR_{11}$；

19)-$C(O)N(R_{11})(R_{12})$；

20)-$C(O)N(R_{11})S(O)_2(R_{12})$；

21)-$N(R_{11})(R_{12})$；

22)-$N(R_{13})C(O)N(R_{11})(R_{12})$；

23)-$N(R_{11})C(O)(R_{12})$；

24)-$N(R_{11})C(O)_2(R_{12})$；

25)-$N(R_{13})S(O)_2N(R_{11})(R_{12})$；

26)-$N(R_{11})S(O)_2(R_{12})$；

27)-OR_{11}；

28)-$OC(O)R_{11}$；

29)-$OC(O)OR_{11}$；以及

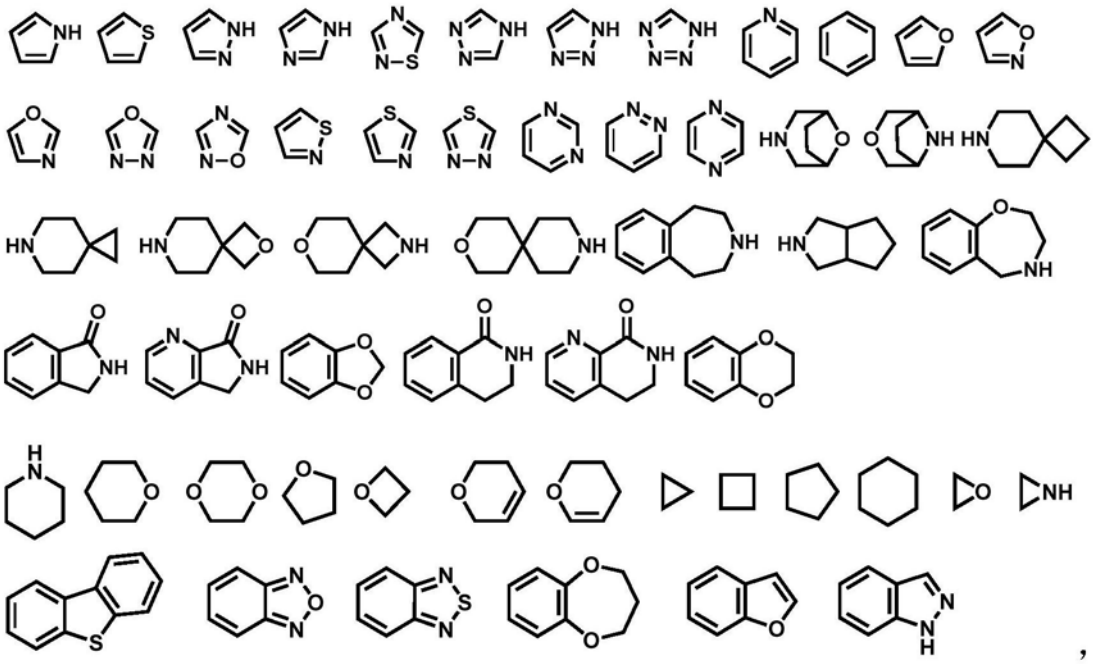
30)-$OC(O)N(R_{11})(R_{12})$；

其中每个R_{11}、R_{12}和R_{13}独立地选自氢、任选取代的-C_1-C_8烷基、任选取代的-C_2-C_8烯基、任选取代的-C_3-C_8环烷基、任选取代的3-至8-元杂环烷基、任选取代的芳基以及任选取代的杂芳基；以及

替代地，R_{11}和R_{12}与它们所连接的氮原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环。

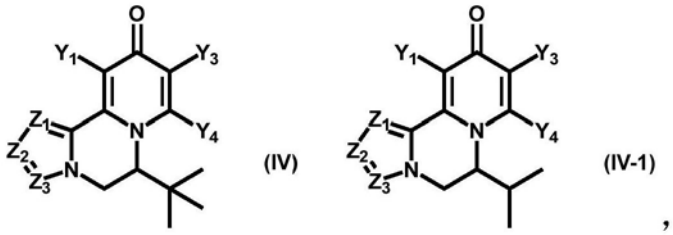
2.根据权利要求1所述的化合物，其中R_1、R_2和R_3各自独立地选自任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基以及任选取代的3-至12-元杂环烷基。

3.根据权利要求1所述的化合物，其中，R_1、R_2和R_3各自独立地选自去掉氢原子的以下中的一种：



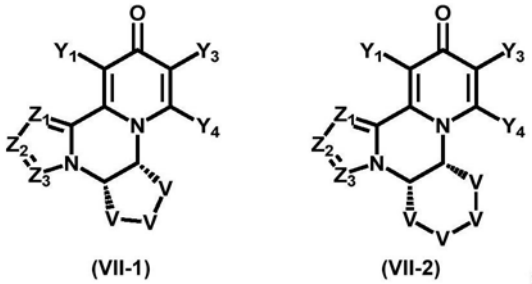
其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代，并且R_{11}和R_{12}如在权利要求1中所定义。

4.根据权利要求1所述的化合物，其由式(IV)～(IV-1)中的一个或其药学上可接受的盐表示：



其中Y_1、Y_3、Y_4、Z_1、Z_2和Z_3如在权利要求1中所定义。

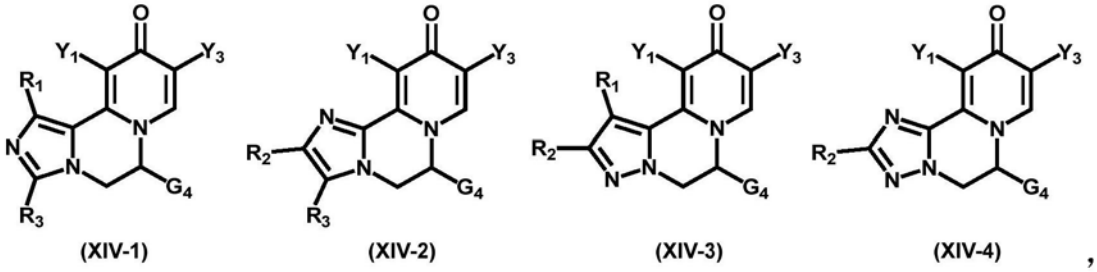
5.根据权利要求1所述的化合物，其由式(VII-1)～(VII-2)中的一个或其药学上可接受的盐表示：



其中一个V是-O-、-C(O)-、-S-、-S(O)$_2$-、-NR_{22}-或-C(R_{22})$_2$-，并且其他V独立地是-O-、-NR_{22}-或-C(R_{22})$_2$-；每个R_{22}独立地是氢、任选取代的-C_1-C_6烷基、任选取代的-C_2-C_6烯基、任选取代的-C_2-C_6炔基、任选取代的C_1-C_6烷氧基；任选取代的-C_3-C_7环烷基、任选取代的3-至7-元杂环、任选取代的芳基或任选取代的杂芳基；替代地，两个相邻的V一起形成-C(R_{22})＝C(R_{22})-，并且Y_1、Y_3、Y_4、Z_1、Z_2和Z_3如在权利要求1中所定义。

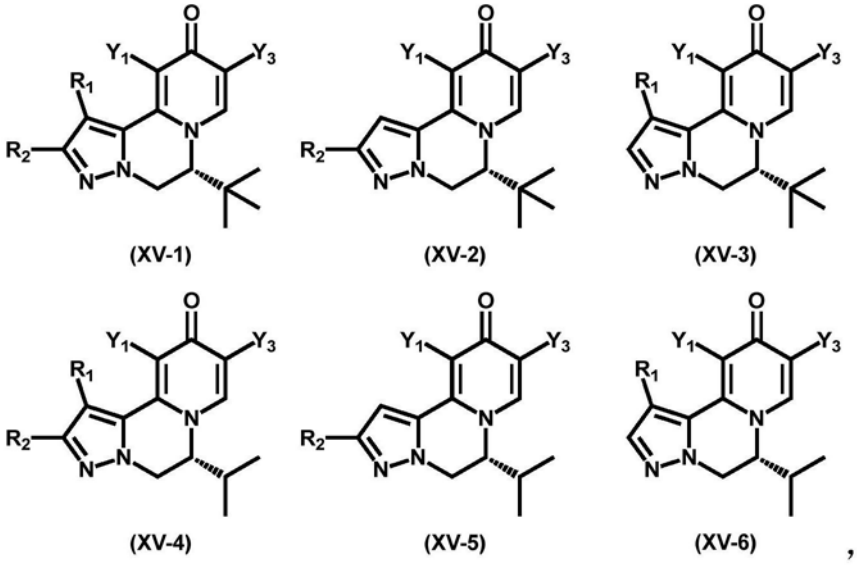
6.根据权利要求1所述的化合物，其由式(XIV-1)～(XIV-4)中的一个或其药学上可接

受的盐表示：



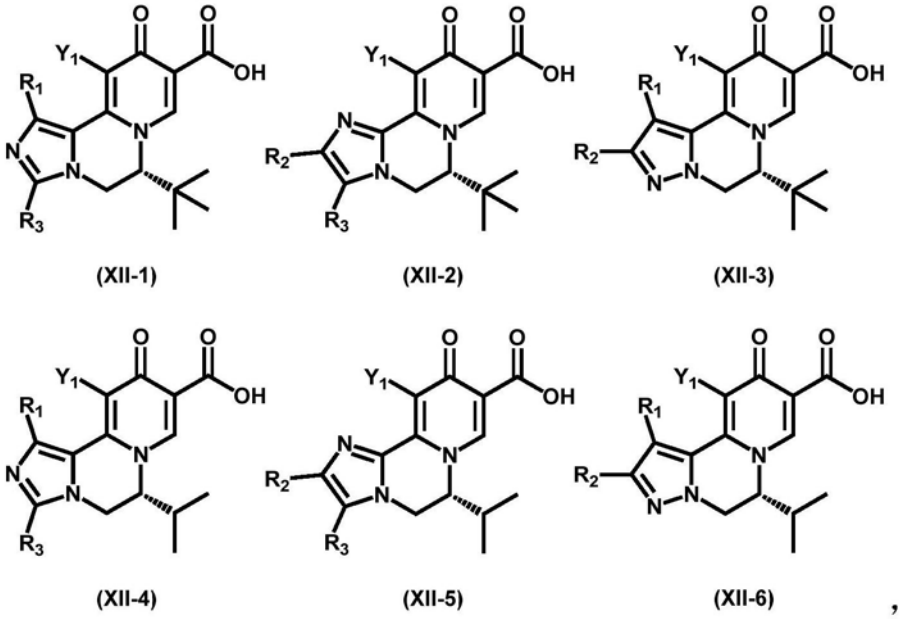
其中Y_1、Y_3、R_1、R_2、R_3和G_4如在权利要求1中所定义。

7.根据权利要求1所述的化合物，其由式(XV-1)～(XV-6)中的一个或其药学上可接受的盐表示：



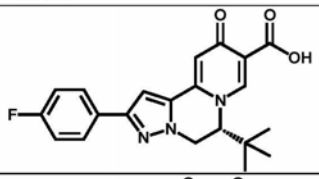
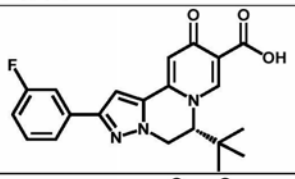
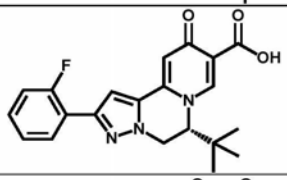
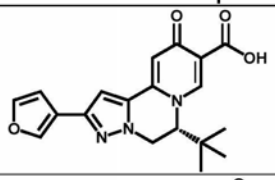
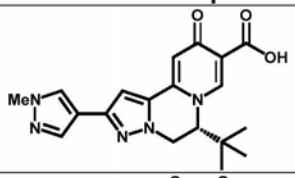
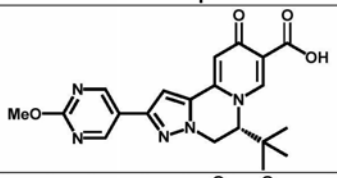
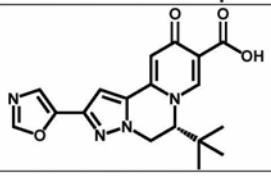
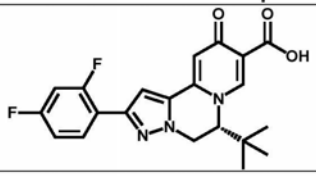
其中Y_1、Y_3、R_1和R_2如在权利要求1中所定义。

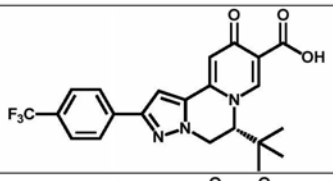
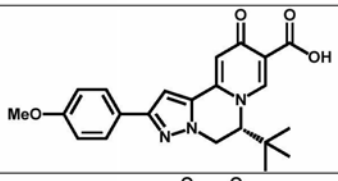
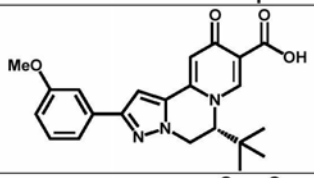
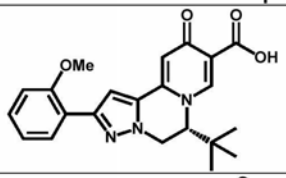
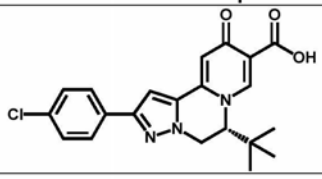
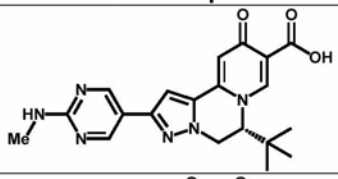
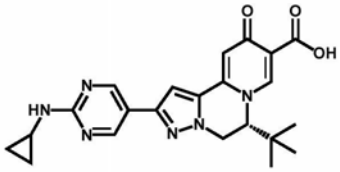
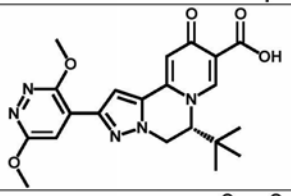
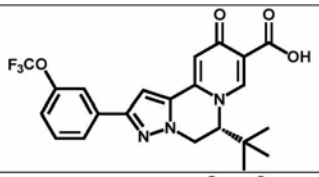
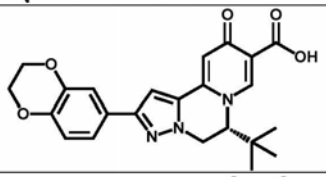
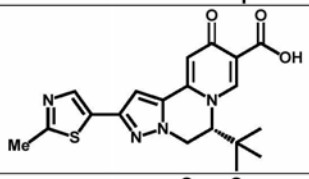
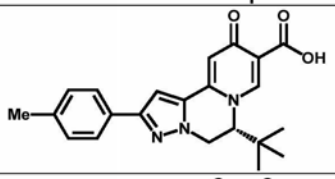
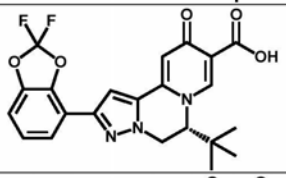
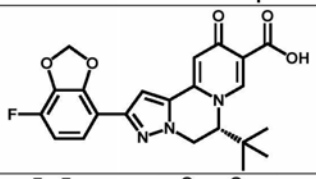
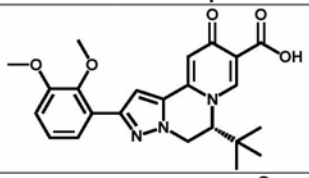
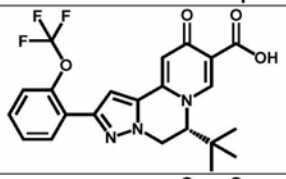
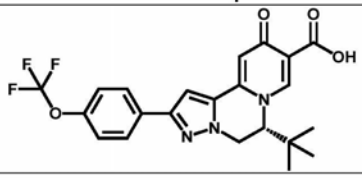
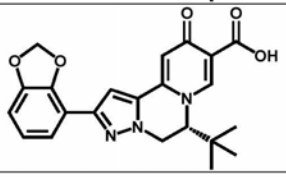
8.根据权利要求1所述的化合物，其由式(XII-1)～(XII-6)中的一个或其药学上可接受的盐表示：

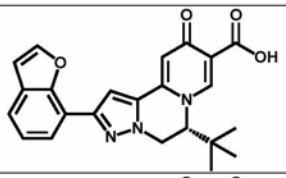
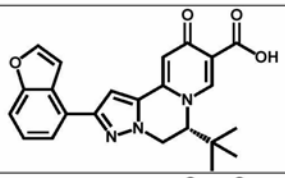
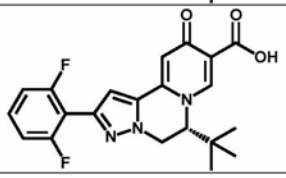
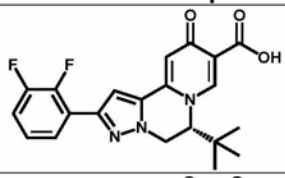
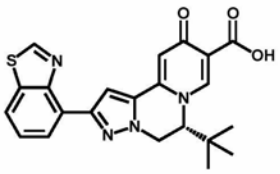
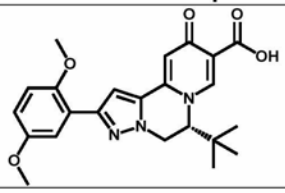
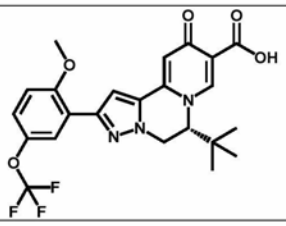
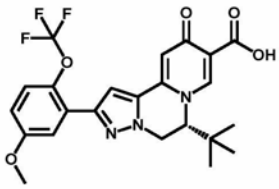
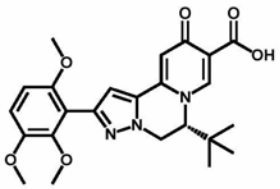
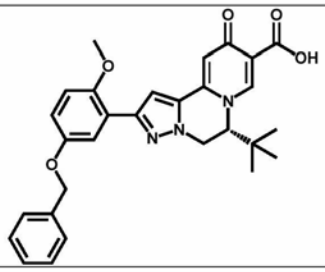
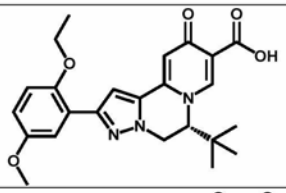
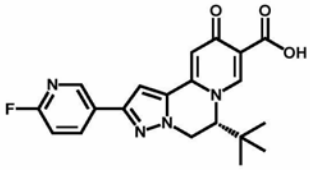
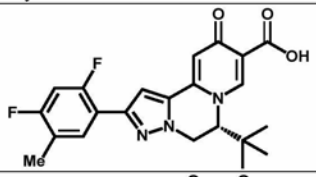
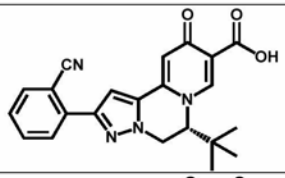
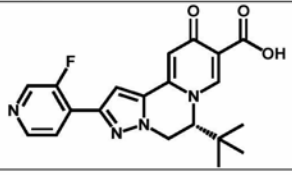
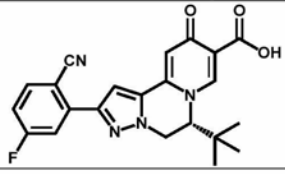


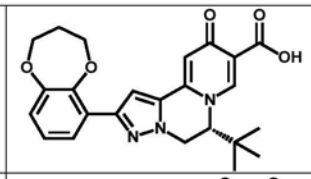
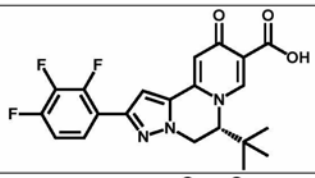
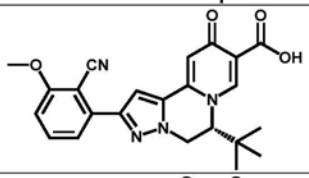
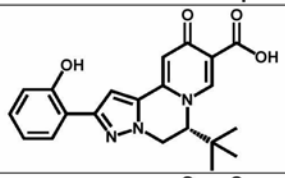
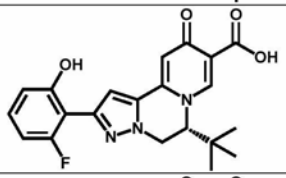
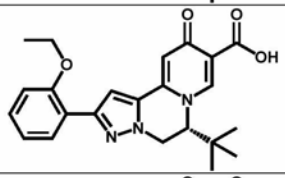
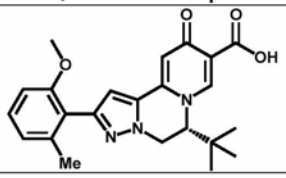
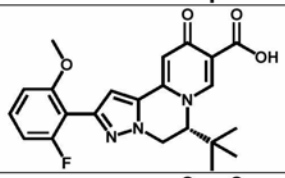
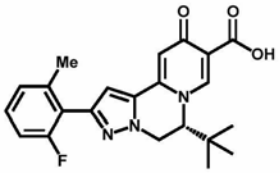
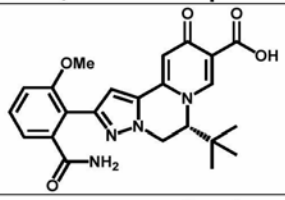
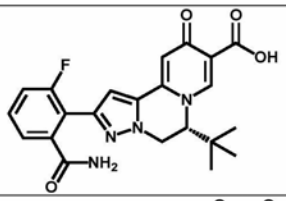
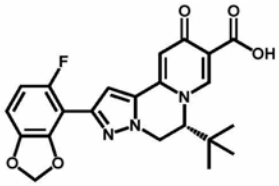
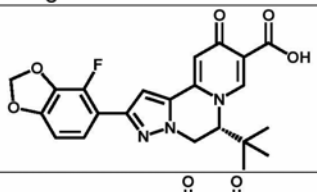
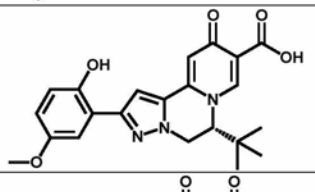
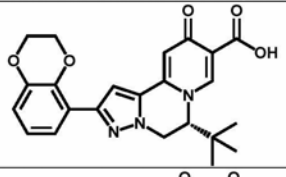
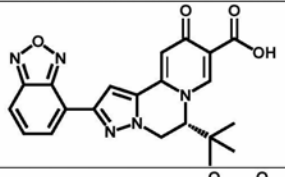
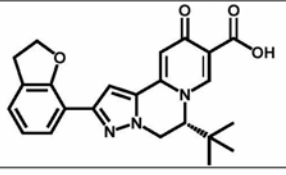
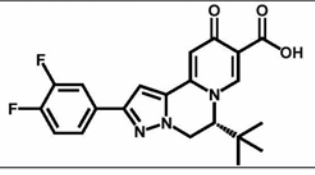
其中Y_1、R_1、R_2和R_3如在权利要求1中所定义。

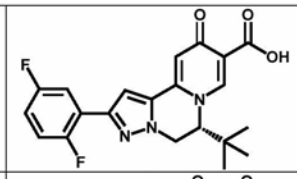
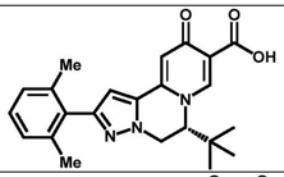
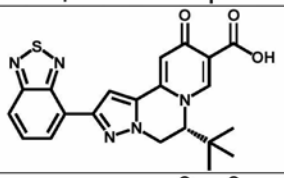
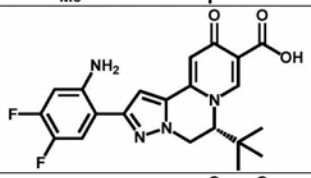
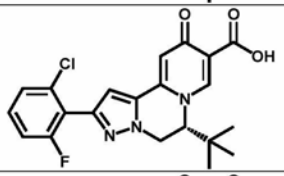
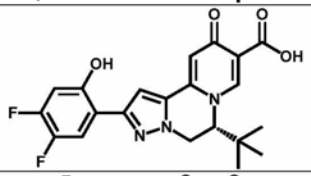
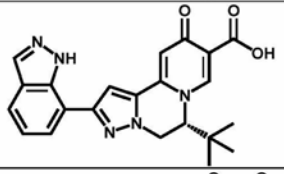
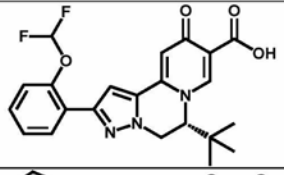
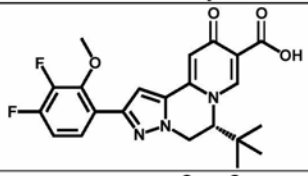
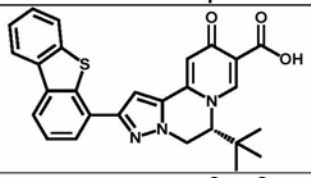
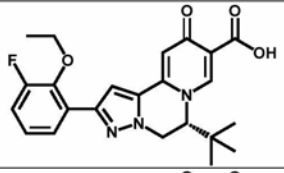
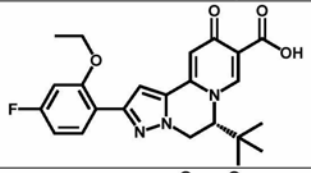
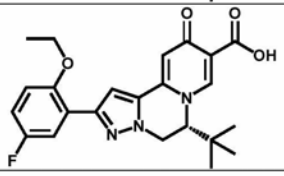
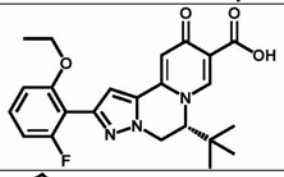
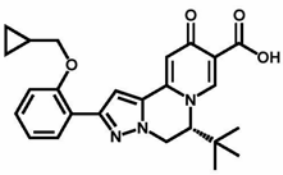
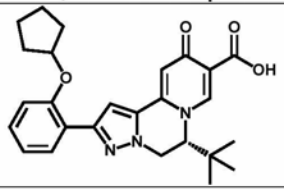
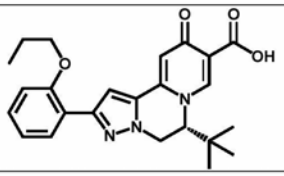
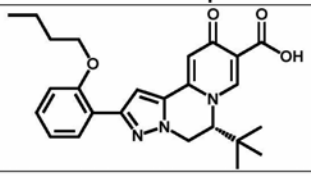
9.根据权利要求1所述的化合物，其选自以下列出的化合物或其药学上可接受的盐：

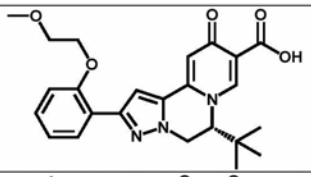
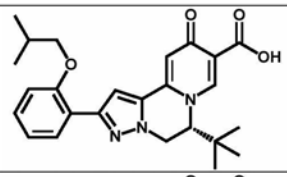
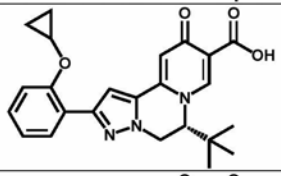
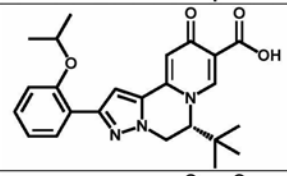
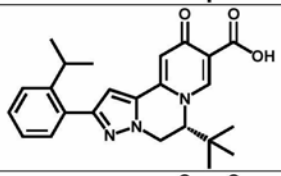
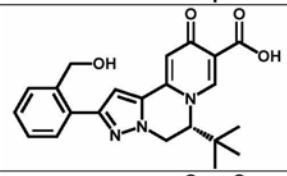
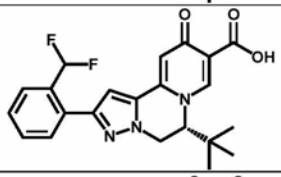
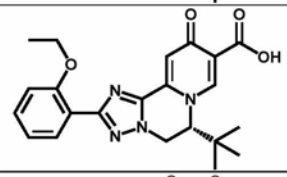
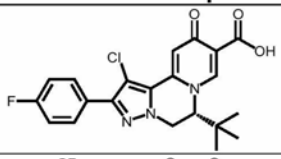
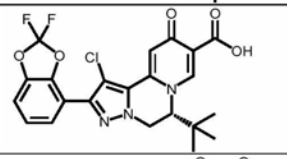
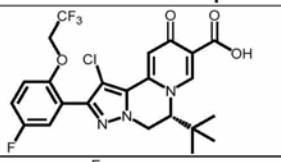
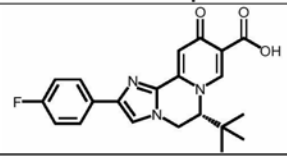
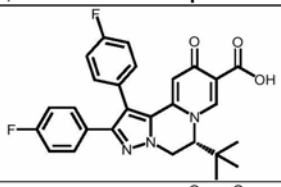
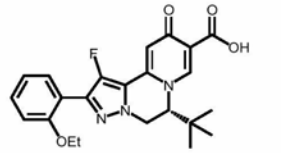
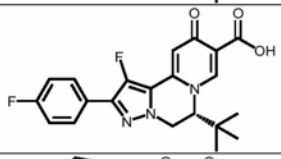
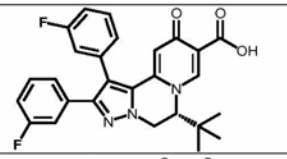
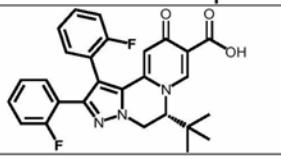
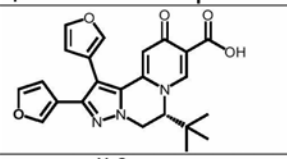
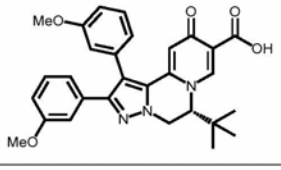
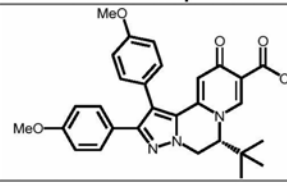
化合物	结构	化合物	结构
1		2	
3		4	
5		6	
7		8	

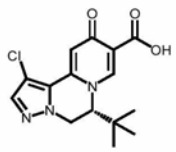
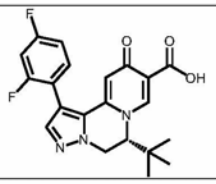
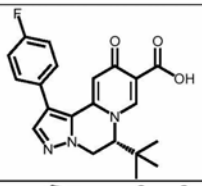
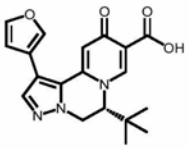
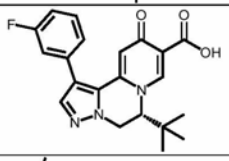
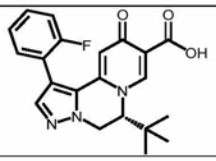
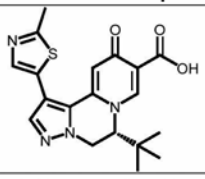
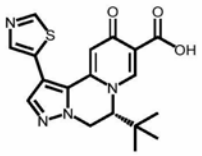
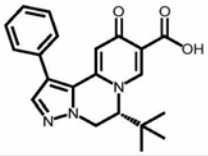
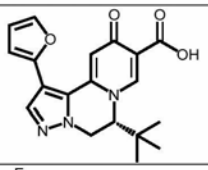
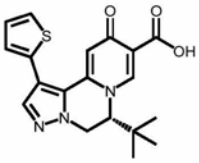
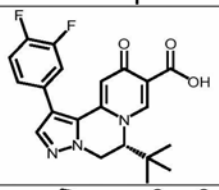
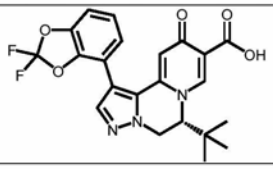
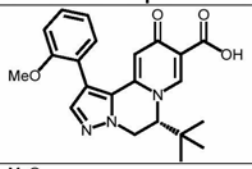
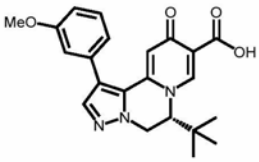
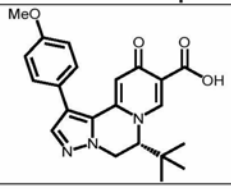
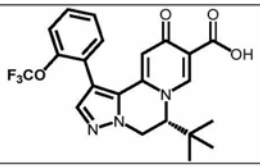
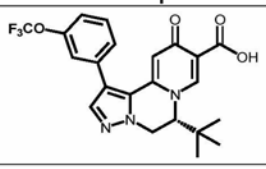
9		10	
11		12	
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	
25		26	

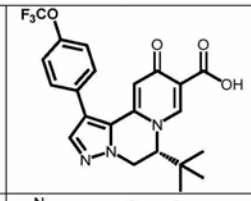
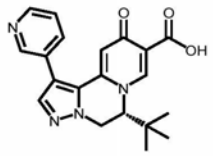
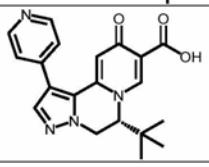
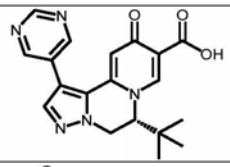
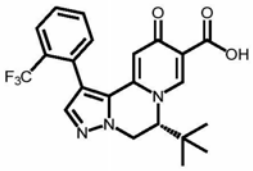
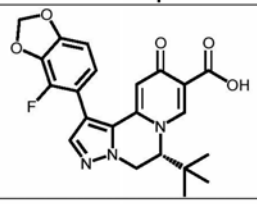
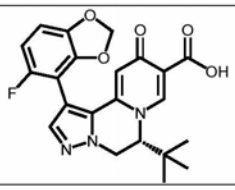
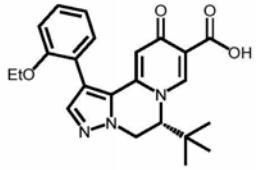
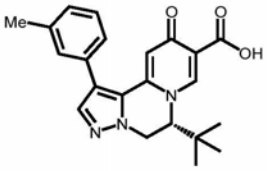
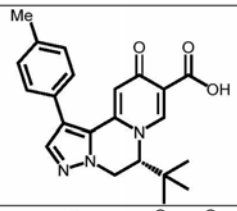
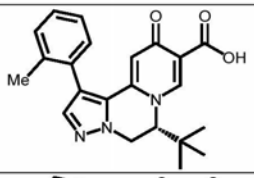
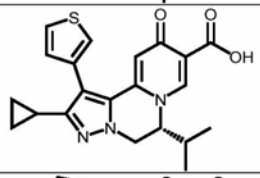
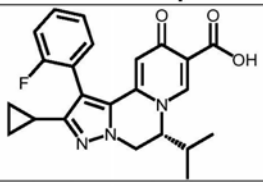
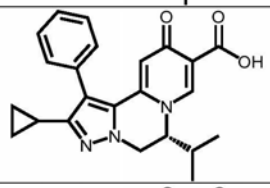
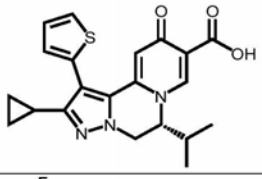
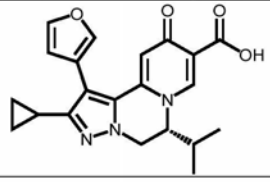
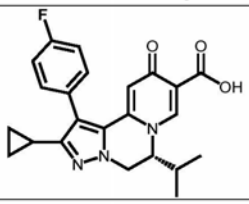
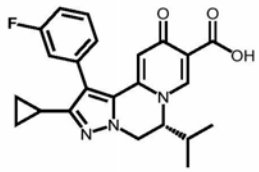
27		28	
29		30	
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	

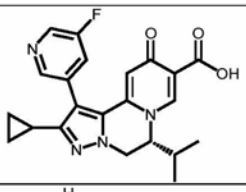
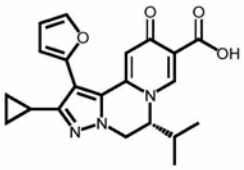
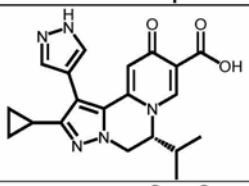
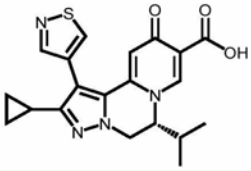
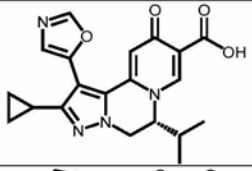
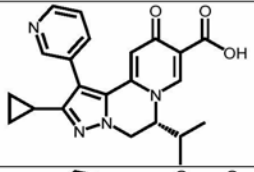
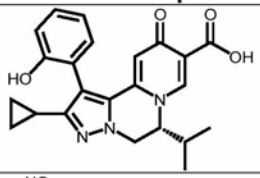
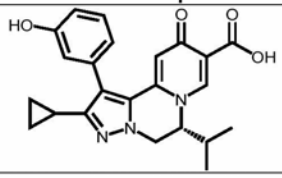
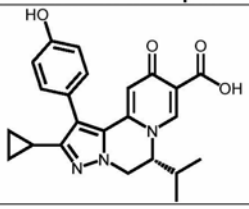
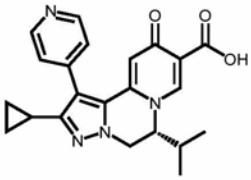
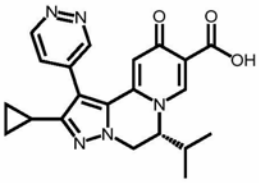
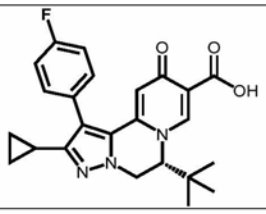
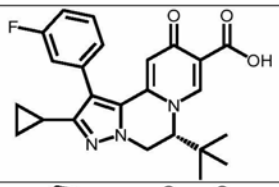
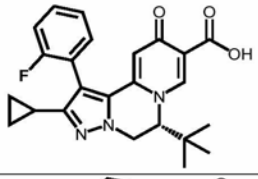
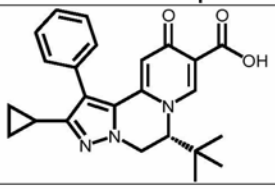
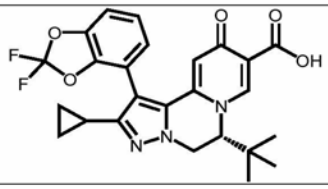
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	
55		56	
57		58	
59		60	

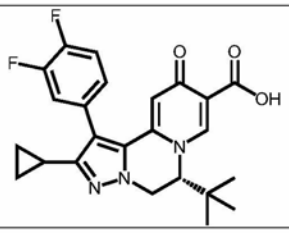
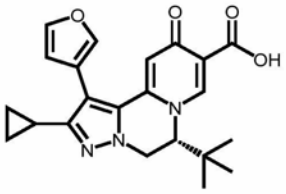
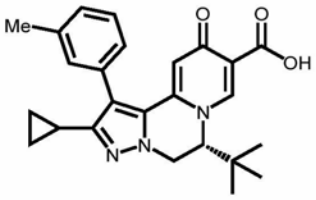
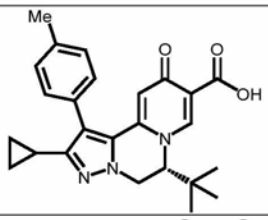
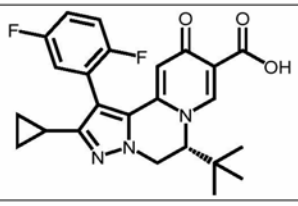
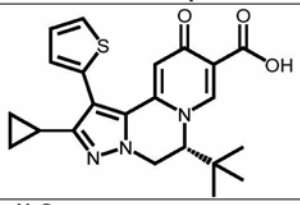
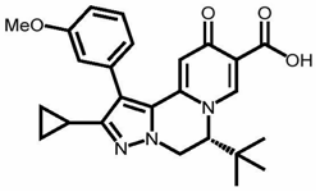
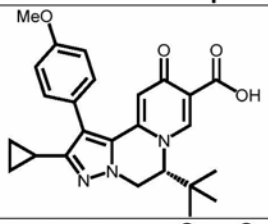
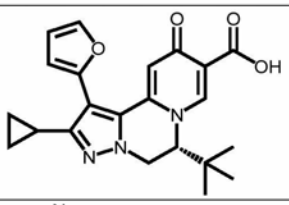
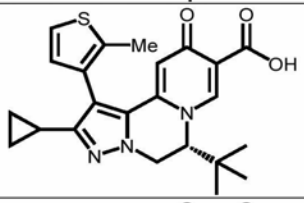
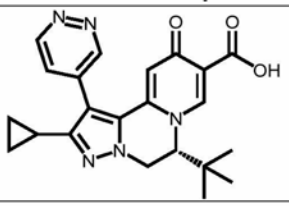
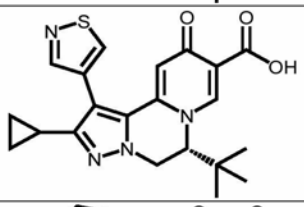
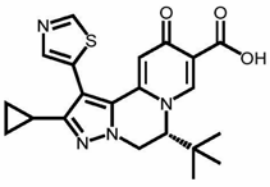
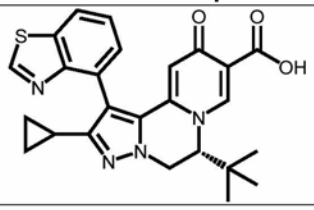
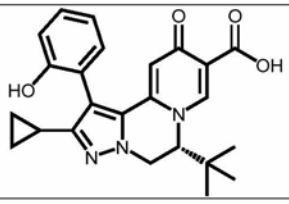
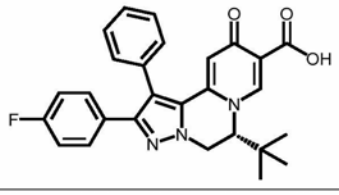
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	
73		74	
75		76	
77		78	

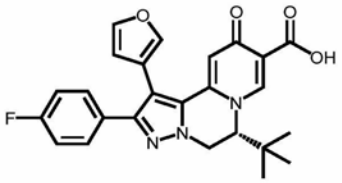
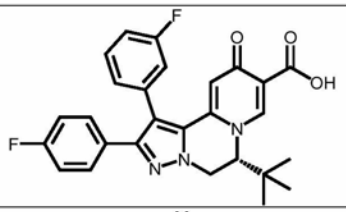
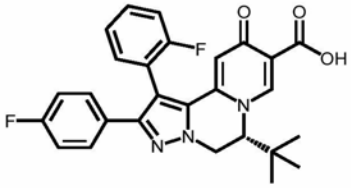
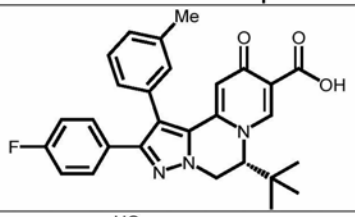
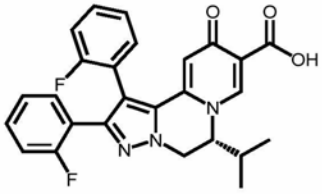
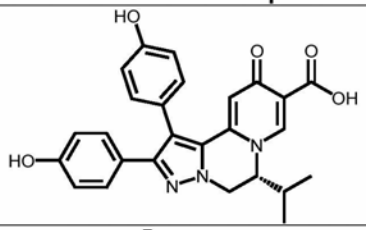
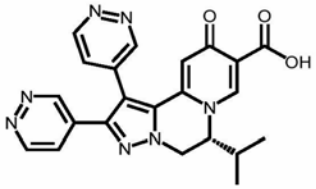
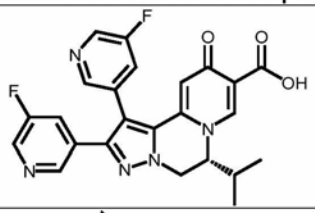
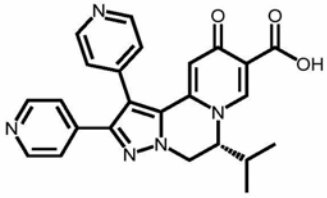
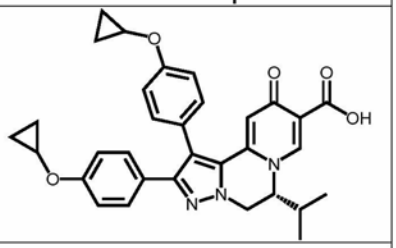
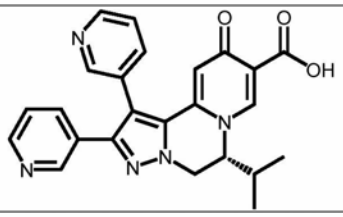
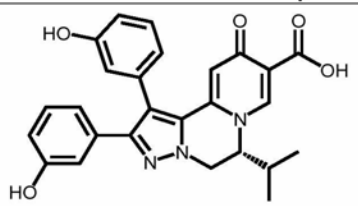
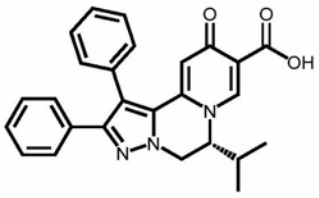
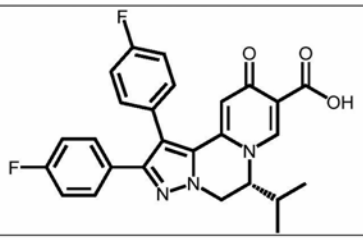
79		80	
81		82	
83		84	
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	
97		98	

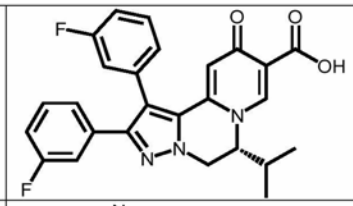
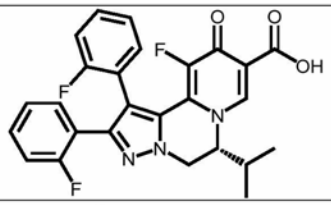
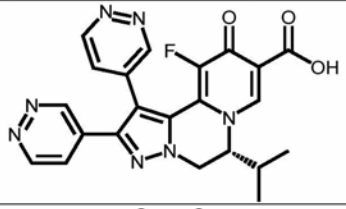
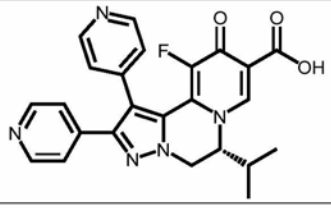
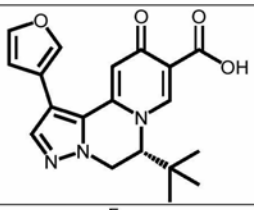
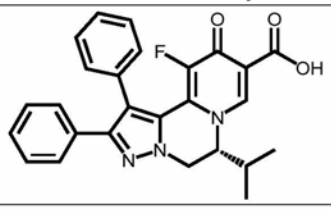
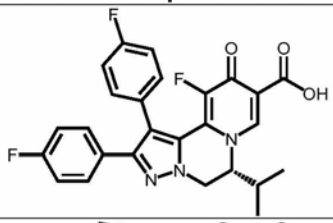
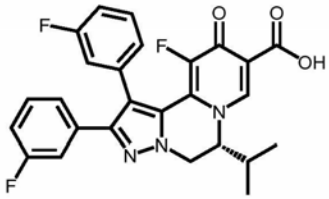
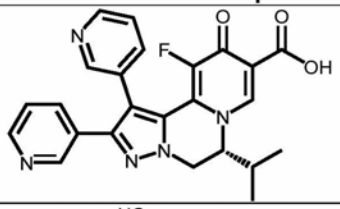
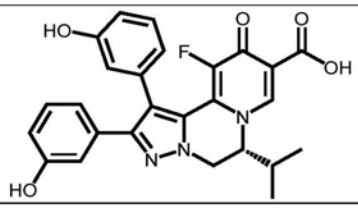
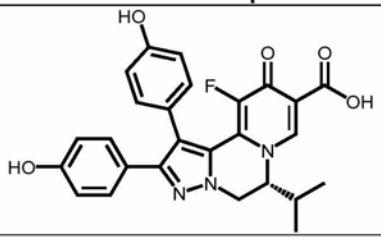
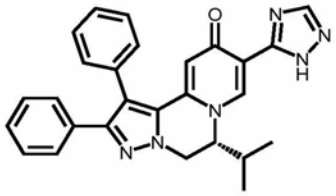
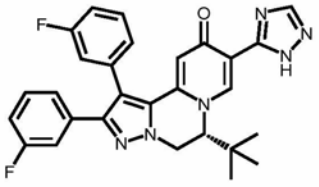
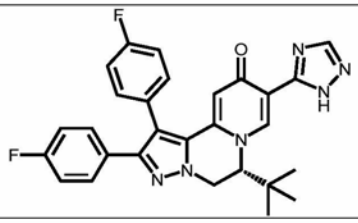
99		100	
101		102	
103		104	
105		106	
107		108	
109		110	
111		112	
113		114	
115		116	

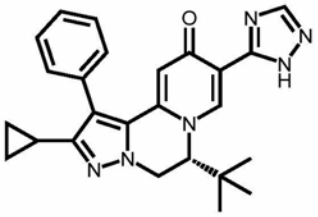
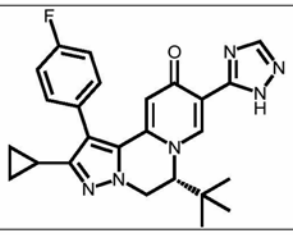
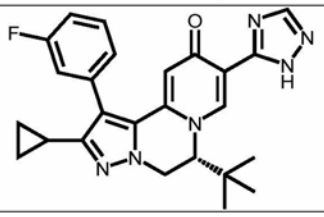
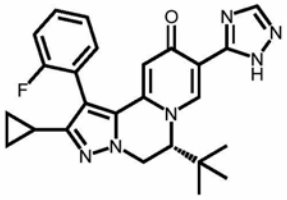
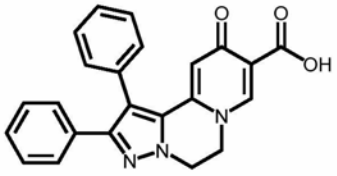
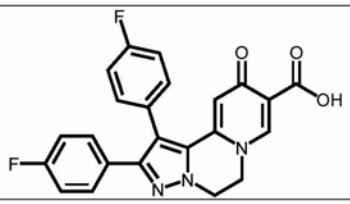
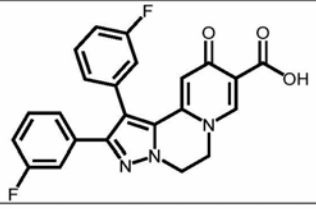
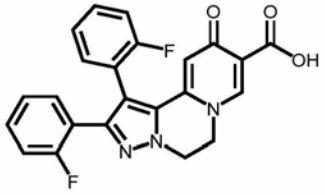
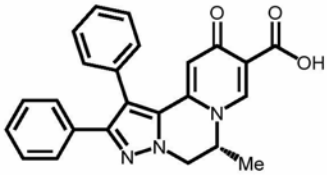
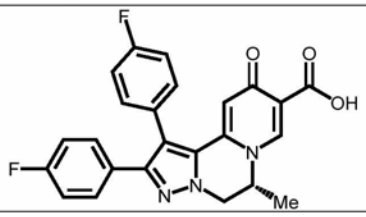
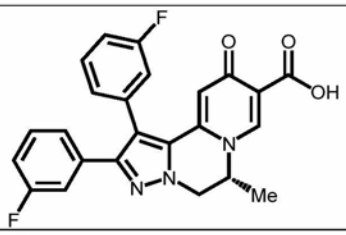
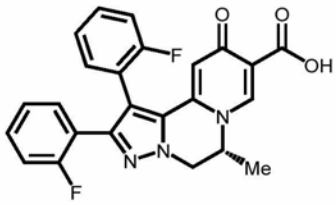
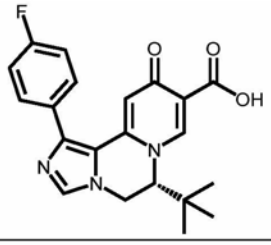
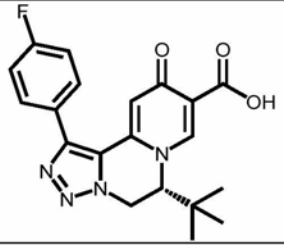
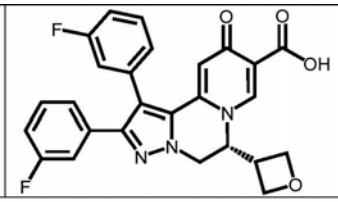
117		118	
119		120	
121		122	
123		124	
125		126	
127		128	
129		130	
131		132	
133		134	

135		136	
137		138	
139		140	
141		142	
143		144	
145		146	
147		148	
149		150	

151		152	
153		154	
155		156	
157		158	
159		160	
161		162	
163		164	
165		166	

167		168	
169		170	
171		172	
173		174	
175		176	
177		178	
179		180	

181		182	
183		184	
185		186	
187		188	
189		190	
191		192	
193		194	

195		196	
197		198	
199		200	
201		202	
203		204	
205		206	
207		208	
209			

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10.一种药物组合物,包括根据权利要求1至9中任一项所述的化合物,所述化合物与药学上可接受的载体或赋形剂联合。

11.一种治疗或预防有此需要的受试者中的HBV感染的方法，包括向所述受试者给药治疗有效量的根据权利要求1至9中任一项所述的化合物或化合物的组合。

12.根据权利要求11所述的方法，进一步包括向所述受试者给药选自由以下组成的组的附加的治疗剂：HBV聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、文献描述的衣壳组装调节剂、逆转录酶抑制剂、TLR-激动剂、细胞病毒RNA传感器的诱导物、治疗性疫苗以及不同或未知机制的剂，及其组合。

13.根据权利要求12所述的方法，其中，所述化合物和所述附加的治疗剂共同配制。

14.根据权利要求12所述的方法，其中，共同给药所述化合物和所述附加的治疗剂。

15.根据权利要求12所述的方法，其中，所述附加的治疗剂以与当单独给药以治疗HBV感染所需的所述附加的治疗剂的剂量或频率相比更低的剂量或频率给药。

16.根据权利要求12所述的方法，其中，所述受试者对选自由HBV聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同的衣壳组装调节剂、细胞病毒RNA传感器的诱导物、治疗性疫苗、不同或未知机制的抗病毒化合物及其组合组成的组的至少一种化合物是难治的。

17.根据权利要求12所述的方法，其中，与给药选自由以下组成的组的化合物相比：HBV聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同的衣壳组装调节剂、细胞病毒RNA传感器的诱导物、治疗性疫苗、不同或未知机制的抗病毒化合物及其组合，所述方法在更大程度上降低所述受试者的病毒载量。

18.根据权利要求12所述的方法，其中，所述方法导致病毒突变和/或病毒抗性的发生率低于用选自由以下组成的组的化合物的治疗：HBV聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同的衣壳组装调节剂、细胞病毒RNA传感器的诱导物、治疗性疫苗、不同或未知机制的抗病毒化合物及其组合。

官能化杂环化合物作为抗病毒剂

[0001] 相关申请

[0002] 本申请要求于2018年11月21日提交的美国临时申请号62/770,428以及于2019年8月8日提交的62/884,486的权益。以上申请的全部教导通过援引并入本文。

技术领域

[0003] 本发明总体上涉及可用作肝炎病毒复制抑制剂的化合物和药物组合物。特别地，本发明涉及可用于治疗病毒感染诸如乙型肝炎病毒(HBV)的四环吡啶酮化合物。本发明提供了如本文公开的新颖的四环吡啶酮化合物，包含这样的化合物的药物组合物，以及在治疗和预防HBV感染中使用这些化合物和组合物的方法。

背景技术

[0004] 全世界超过2.4亿人慢性感染乙型肝炎病毒(HBV)。在此患者群体中，至少2百万居住在美国。对于慢性感染的那些人，许多人将由肝硬化或肝细胞癌(HCC)发展为肝病的并发症。

[0005] HBV是嗜肝DNA病毒家族的成员，并且它能够通过RNA中间体的逆转录进行复制。3.2-kb HBV基因组以具有四个重叠开放阅读框(ORF)的环状、部分双链的DNA构象(rcDNA)存在。这些编码病毒的核心、聚合酶、包膜和X蛋白。在转录病毒RNA之前，必须将rcDNA在细胞中转化为共价闭合环状DNA(cccDNA)。由于rcDNA在转录上是惰性的，因此cccDNA是HBV转录的唯一模板，并且它的存在是感染所需的。

[0006] HBV病毒包膜包含表面抗原蛋白(HBsAg)的混合物。HBsAg外壳包含共享公共区域的三种蛋白质，该区域包括三种蛋白质中最小的一种(SHBsAg)。其他两种蛋白质(中等的HBsAg(MHBsAg)和大的HBsAg(LHBsAg))两者都包含具有附加多肽片段的SHBsAg片段。SHBsAg、MHBsAg和LHBsAg也可以组装成包含与在感染性病毒颗粒周围发现的相同的蛋白质的非感染性亚病毒颗粒，称为22-nm颗粒。由于22-nm颗粒包含与在感染性HBV病毒粒子周围存在的相同的抗原表面蛋白，因此它们可用作疫苗以产生中和抗体。

[0007] 在慢性感染的患者中，发现非感染性22-nm颗粒比感染性病毒粒子的丰度大得多。作为结果，22-nm颗粒被认为能够保护感染性病毒粒子免受感染的宿主的免疫应答。它们不仅可以充当感染性诱饵，而且它们还可以抑制免疫细胞的正常运行，从而损害宿主对HBV的免疫应答。因此，降低亚病毒颗粒的水平是治疗HBV感染的可行治疗方法。(参考WO2015/13990)。

[0008] 在临床环境中，慢性HBV感染的诊断标志是高血清HBsAg水平。近年来，数据已经表明持续病毒学应答(SVR)与早期治疗期间HBsAg下降对应，而持续暴露于HBsAg和其他病毒抗原可能导致不适当的免疫原性。显示血清HBsAg降低更高的患者在治疗后达到了相当较高的SVR。

[0009] 用于慢性感染HBV的患者的当前治疗选项在数量和范围上受到限制。它们包括干扰素疗法和基于核苷的HBV DNA聚合酶抑制剂，即恩替卡韦(entecavir)和替诺福韦

(tenofovir)。当前的护理标准致力于降低病毒血症和允许的肝功能障碍的水平,但是与不良副作用相关,并且增加了耐药性HBV突变体的持久性。当前疗法的显著缺点是它们无法消除cccDNA的肝储液(hepatic resevoirs),无法阻止cccDNA中的HBsAg转录,或无法限制HBsAg进入血清的分泌,这将最终扼杀免疫应答。尽管已报道降低血清HBsAg水平的化合物,但它们尚未被批准为HBV疗法。(参考WO2015/113990、WO2015/173164、WO2016/023877、WO2016/071215、WO2016/128335、WO 2017/140821、WO 2019097479、WO 2019166951、WO 2019123285、WO 2018198079、WO 2018073753、WO 2018047109、WO 2019110352、WO 2019129681、WO 2018087345、WO 2018083136、WO 2018083106、WO 2018083081、WO 2017216391、WO 2018001952、WO 2018001944、WO 2016107832、WO 2016177655、WO 2017017042、WO 2017017043、WO 2017013046、WO 2016128335、WO 2016071215、WO 2015173164、WO 2015113990、WO 2018219356、WO 2018130152、WO 2018154466、WO 2019069293、WO 2017061466、WO 2018181883、WO 2018161960、WO 2017205115、WO 2018144605、WO 2018085619、WO 2018019297以及WO 2018022282)。

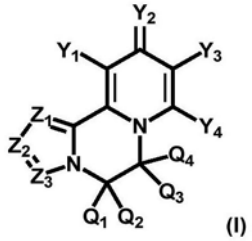
[0010] 由于这种高度未满足的临床需求,因此需要用于慢性HBV感染的更有效的疗法。本发明描述了据信抑制包含HBsAg的亚病毒颗粒分泌的化合物的制备方法和使用方法。这种类型的化合物可以用于治疗HBV感染并减少肝病并发症(诸如肝硬化或HCC)的发生。

[0011] 本领域需要治疗、改善或预防HBV感染的新颖的治疗剂。将这些治疗剂作为单一疗法或与其他HBV治疗或辅助治疗联合给药于HBV感染的患者,将导致显著改善的预后、疾病进展的减少和血清转化率的提高。

发明内容

[0012] 本发明涉及新颖的抗病毒化合物、包括这样的化合物的药物组合物,以及用所述化合物治疗或预防需要这样的疗法的受试者中的病毒(特别是HBV)感染的方法。本发明的化合物抑制由乙型肝炎病毒(HBV)编码的一种或多种蛋白质或干扰HBV的生命周期,并且还可用作抗病毒剂。另外,本发明提供了用于制备所述化合物的方法。

[0013] 本发明提供了由式(I)表示的化合物,

[0014] 

(I)

[0015] 及其药学上可接受的盐、N-氧化物、酯和前药,其中:

[0016] Q_1、Q_2、Q_3和Q_4各自独立地选自氢、卤素、$NR_{11}R_{12}$、任选取代的-C_1-C_6烷基、任选取代的-C_1-C_6烷氧基、任选取代的-C_3-C_8环烷基;任选取代的-C_3-C_8环烯基;任选取代的3-至8-元杂环烷基;任选取代的芳基;以及任选取代的杂芳基;

[0017] 替代地,Q_1和Q_2中的一个和Q_3和Q_4中的一个与它们所连接的碳原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环或碳环;

[0018] 替代地,Q_1和Q_2与它们所连接的碳原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环或碳环;

[0019] 替代地，Q_3和Q_4与它们所连接的碳原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环或碳环；

[0020] Y_1是氢、卤素或任选取代的C_1-C_6烷基；

[0021] Y_2是O、NR_{11}、$N(OR_{11})$或$N(NR_{11})$；

[0022] Y_3是$-COOR_{11}$、$-C(O)NHSO_2R_{11}$、$-C(O)NHSO_2NR_{11}R_{12}$或1,2,4-噁二唑-3-基-5(4H)-酮，或Y_3是任选取代的芳基、任选取代的杂芳基、任选取代的$-C_5$-C_6环烷基或任选取代的5-至6-元杂环烷基；

[0023] Y_4是氢或任选取代的甲基；

[0024] 替代地，Y_2和Y_3一起形成包含1、2或3个双键的任选取代的5-12元杂环；

[0025] Z_1是N或CR_1，Z_2是N或CR_2，并且Z_3是N或CR_3，前提是Z_1、Z_2和Z_3中的至少一个是N；

[0026] R_1、R_2和R_3各自独立地选自：

[0027] 1)氢；

[0028] 2)卤素；

[0029] 3)$-NO_2$；

[0030] 4)氰基；

[0031] 5)任选取代的$-C_1$-C_8烷基；

[0032] 6)任选取代的$-C_2$-C_8烯基；

[0033] 7)任选取代的$-C_2$-C_8炔基；

[0034] 8)任选取代的$-C_3$-C_8环烷基；

[0035] 9)任选取代的3-至12-元杂环烷基；

[0036] 10)任选取代的芳基；

[0037] 11)任选取代的芳基烷基；

[0038] 12)任选取代的杂芳基；

[0039] 13)任选取代的杂芳基烷基；

[0040] 14)$-SR_{11}$；

[0041] 15)$-S(O)_2R_{11}$；

[0042] 16)$-S(O)_2N(R_{11})(R_{12})$；

[0043] 17)$-C(O)R_{11}$；

[0044] 18)$-C(O)OR_{11}$；

[0045] 19)$-C(O)N(R_{11})(R_{12})$；

[0046] 20)$-C(O)N(R_{11})S(O)_2(R_{12})$；

[0047] 21)$-N(R_{11})(R_{12})$；

[0048] 22)$-N(R_{13})C(O)N(R_{11})(R_{12})$；

[0049] 23)$-N(R_{11})C(O)(R_{12})$；

[0050] 24)$-N(R_{11})C(O)_2(R_{12})$；

[0051] 25)$-N(R_{13})S(O)_2N(R_{11})(R_{12})$；

[0052] 26)$-N(R_{11})S(O)_2(R_{12})$；

[0053] 27)$-OR_{11}$；

[0054] 28)$-OC(O)R_{11}$；

[0055] 29)-OC(O)OR_{11};以及

[0056] 30)-OC(O)N(R_{11})(R_{12});

[0057] 其中R_{11}、R_{12}和R_{13}各自独立地选自氢、任选取代的-C_1-C_8烷基、任选取代的-C_2-C_8烯基、任选取代的-C_3-C_8环烷基、任选取代的3-至8-元杂环烷基、任选取代的芳基以及任选取代的杂芳基。替代地,R_{11}和R_{12}与它们所连接的氮原子一起形成包含0、1、2或3个双键的任选取代的3-8元杂环。优选地,R_2是任选取代的芳基、任选取代的杂芳基或任选取代的双环杂环烷基,更优选地任选取代的芳基或任选取代的杂芳基。

[0058] 优选地,R_1是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至12-元杂环烷基;并且R_2是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至12-元杂环烷基。

[0059] 在某些实施方式中,Z_3是N,Z_1是CR_1并且Z_2是CR_2,并且R_2不是氢;卤素;氰基;任选取代的-C_1-C_6烷基;任选取代的-C_3-C_7环烷基;任选取代的3-至7-元杂环烷基;-NH_2;-NHC_1-C_6烷基;-OH;或-OC_1-C_6烷基。在这种实施方式中,R_2优选地是任选取代的芳基、任选取代的杂芳基、任选取代的芳基烷基或任选取代的杂芳基烷基,并且R_1优选地是任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、氢或卤素。

[0060] 上述每个优选的基团可以与一个、任何或所有其他优选的基团组合。

具体实施方式

[0061] 在本发明的一种实施方式中,是如上所述的式(I)的化合物或及其药学上可接受的盐。

[0062] 在某些实施方式中,本发明涉及式(I)的化合物,及其药学上可接受的盐,其中Y_1是氢、F、Cl、-CH_3或-CF_3。优选地,Y_1是H或F。

[0063] 在某些实施方式中,本发明涉及式(I)的化合物,及其药学上可接受的盐,其中Y_2是O。

[0064] 在某些实施方式中,本发明涉及式(I)的化合物,及其药学上可接受的盐,其中Y_3是-COOH或-C(O)NHSO_2N$R_{11}R_{12}$,或Y_3是三唑基,其中R_{11}和R_{12}如先前所定义。

[0065] 在某些实施方式中,本发明涉及式(I)的化合物,及其药学上可接受的盐,其中Y_4是氢或CH_3。

[0066] 在某些实施方式中,本发明涉及式(I)的化合物,及其药学上可接受的盐,其中R_1、R_2和R_3中的至少一个,优选地R_2是任选取代的芳基;任选取代的芳基烷基;任选取代的杂芳基;或任选取代的杂芳基烷基。

[0067] 在某些实施方式中,Z_3是N,Z_2是CR_2,并且Z_1是CR_1,其中R_1和R_2如上所定义。在某些实施方式中,R_1是氢或卤素,优选地氢。在某些实施方式中,R_2是任选取代的芳基;任选取代的芳基烷基;任选取代的杂芳基;或任选取代的杂芳基烷基。

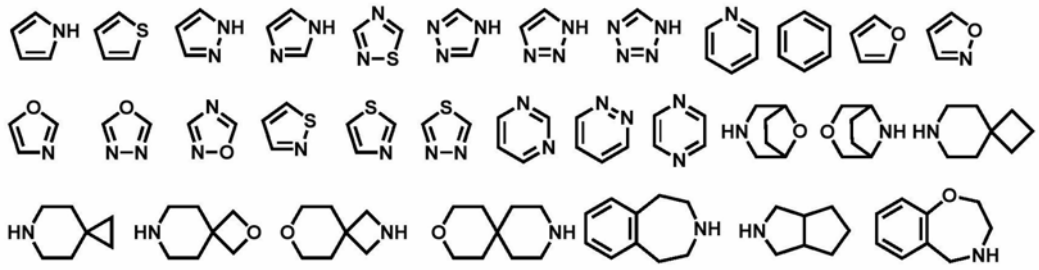
[0068] 在某些实施方式中,Z_3是N,Z_1是CR_1,并且Z_2是CR_2,其中R_1是任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基或任选取代的3-至12-元杂环烷基;并且R_2如先前所定义。优选地,R_1是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基;并且R_2如先前所定义。更优选地,R_1是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选

取代的3-至8-元杂环烷基;并且R_2是氢。

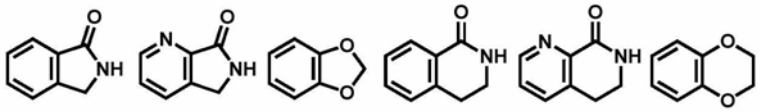
[0069] 在某些实施方式中,Z_3是N,Z_1是CR_1,并且Z_2是CR_2,其中R_2是任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基或任选取代的3-至12-元杂环烷基;并且R_1如先前所定义。优选地,R_2是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基;并且R_1如先前所定义。更优选地,R_2是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基;并且R_1是氢。

[0070] 在某些实施方式中,Z_3是N,Z_1是CR_1,并且Z_2是CR_2,其中R_1是任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基或任选取代的3-至12-元杂环烷基;并且R_2是任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基或任选取代的3-至12-元杂环烷基。优选地,R_1是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基;并且R_2是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基。

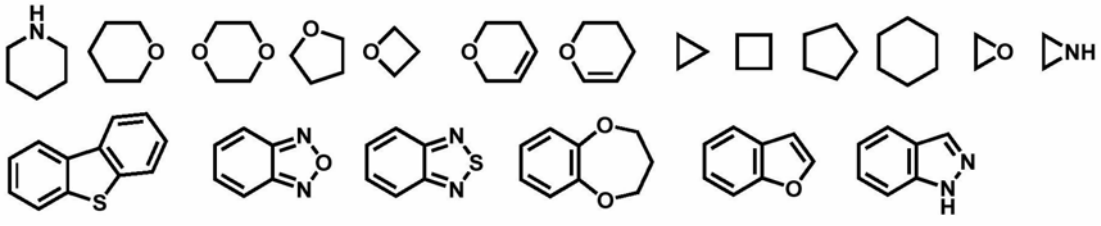
[0071] 在某些实施方式中,本发明涉及式(I)的化合物,及其药学上可接受的盐,其中R_1、R_2和R_3中的至少一个,优选地R_1和R_2中的至少一个衍生自去掉氢原子的以下中的一种:



[0072]



,或

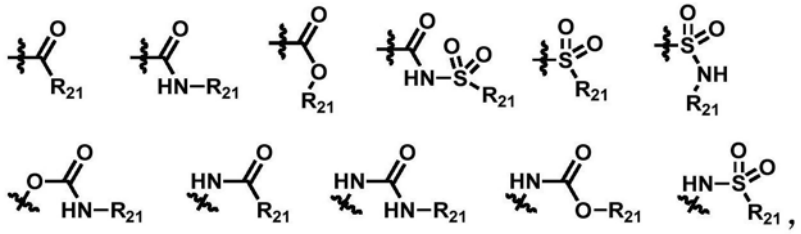


,

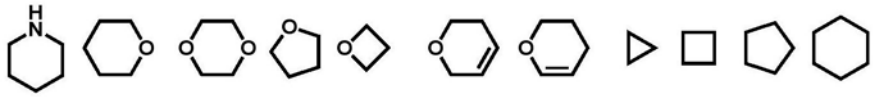
[0073] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

[0074] 在某些实施方式中,本发明涉及式(I)的化合物,及其药学上可接受的盐,其中R_1、R_2和R_3中的至少一个,优选地R_1和R_2中的至少一个选自以下中的一种:

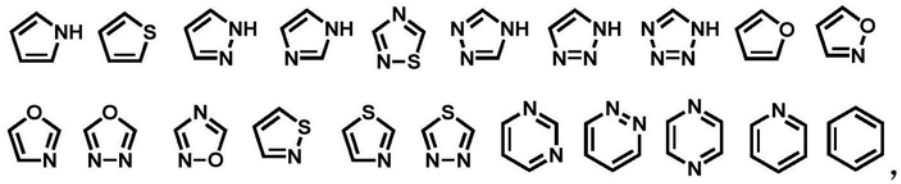
[0075]



[0076] 其中每个R_{21}独立地选自-CH_3、-异丙基、-叔丁基或去掉氢原子的以下中的一种：



[0077]

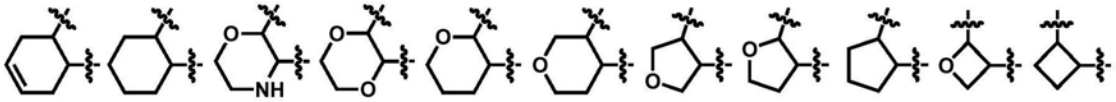


[0078] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

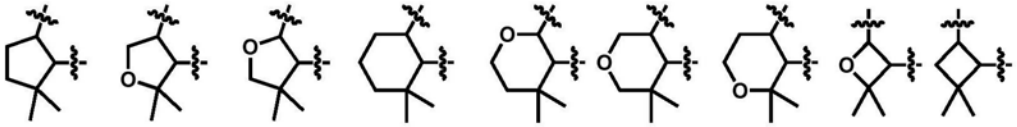
[0079] 在某些实施方式中，本发明涉及式(I)的化合物，及其药学上可接受的盐，其中Q_1是氢、Cl或F；Q_2是氢、Cl或F，并且Q_3是氢、Cl或F。

[0080] 在某些实施方式中，本发明涉及式(I)的化合物，及其药学上可接受的盐，其中Q_4是-叔丁基或异丙基。

[0081] 在某些实施方式中，本发明涉及式(I)的化合物，及其药学上可接受的盐，其中Q_4与Q_1或Q_2以及与它们所连接的哌啶基环上的碳原子一起形成选自以下的任选取代的环：

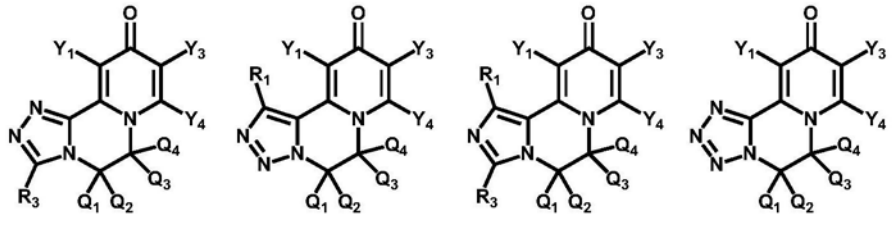


[0082]

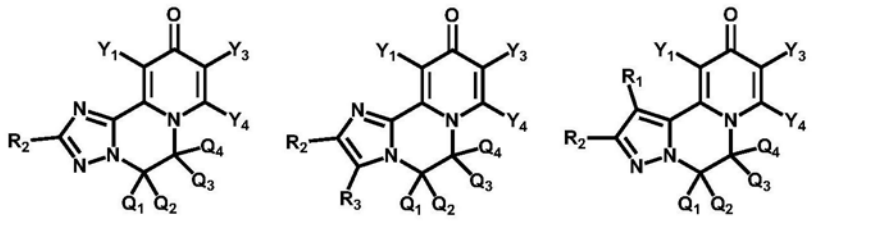


[0083] 在某些实施方式中，式(I)的化合物由式(II-1)～(II-7)中的一个或其药学上可接受的盐表示：

[0084]



(II-1) (II-2) (II-3) (II-4)

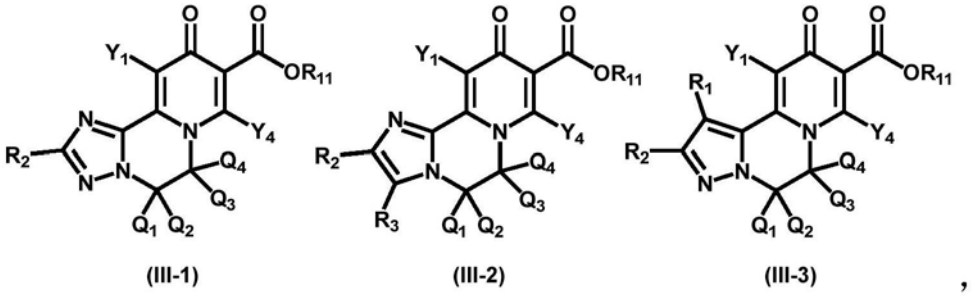


(II-5) (II-6) (II-7)

[0085] 其中Y_1、Y_3、Y_4、R_1、R_2、R_3、Q_1、Q_2、Q_3和Q_4如先前所定义。在某些实施方式中，Q_3和Q_4与它们所连接的碳原子一起形成螺环。在某些实施方式中，Q_1和Q_3两者均为氢，并且Q_2和Q_4与它们所连接的碳原子一起形成顺式稠环。

[0086] 在另一种实施方式中，式(I)的化合物由式(III-1)或式(III-2)或式(III-3)或其

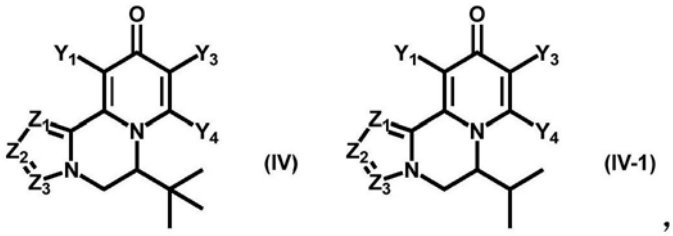
药学上可接受的盐表示：

[0087] 

，

[0088] 其中Y_1、Y_4、R_1、R_2、R_3、R_{11}、Q_1、Q_2、Q_3和Q_4如先前所定义。

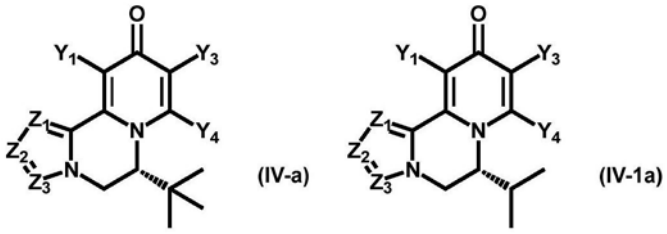
[0089] 在另一种实施方式中，式(I)的化合物由式(IV)或式(IV-1)或其药学上可接受的盐表示：

[0090] 

，

[0091] 其中Y_1、Y_3、Y_4、Z_1、Z_2和Z_3如先前所定义。

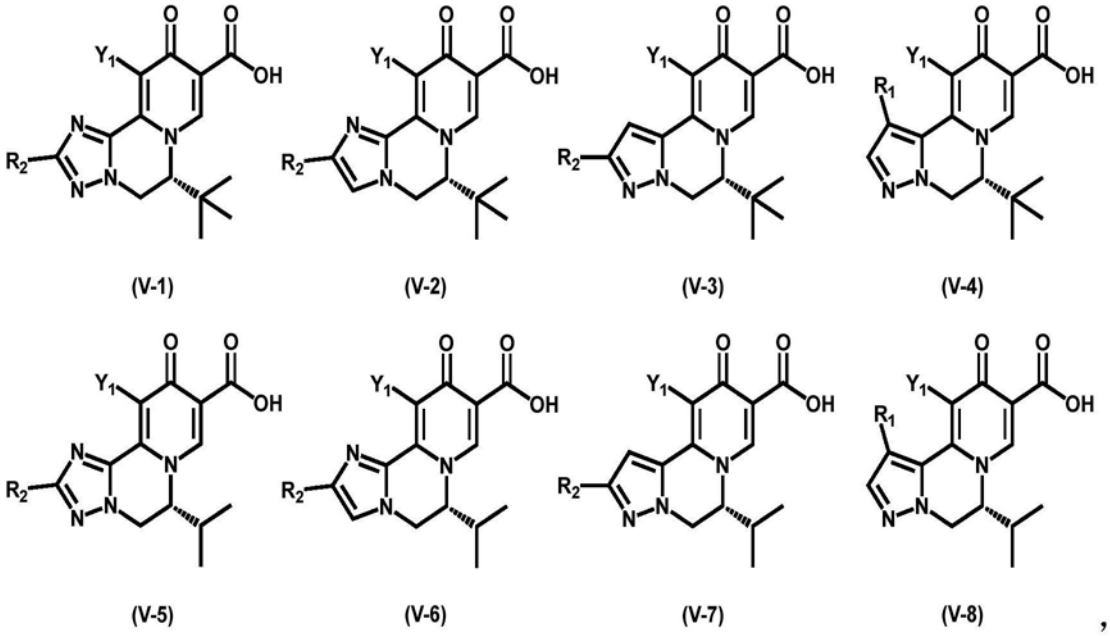
[0092] 在另一种实施方式中，式(I)的化合物由式(IV-a)或式(IV-1a)或其药学上可接受的盐表示：

[0093] 

，

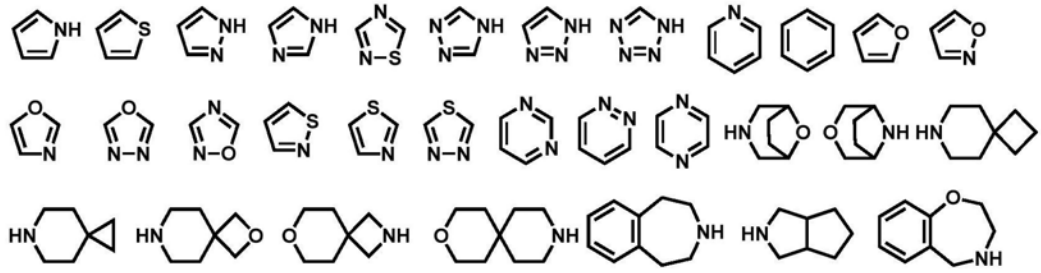
[0094] 其中Y_1、Y_3、Y_4、Z_1、Z_2和Z_3如先前所定义。

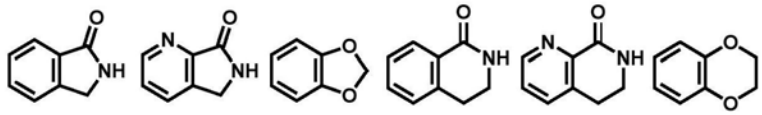
[0095] 在另一种实施方式中，式(I)的化合物由式(V-1)～式(V-8)中的一个或其药学上可接受的盐表示：

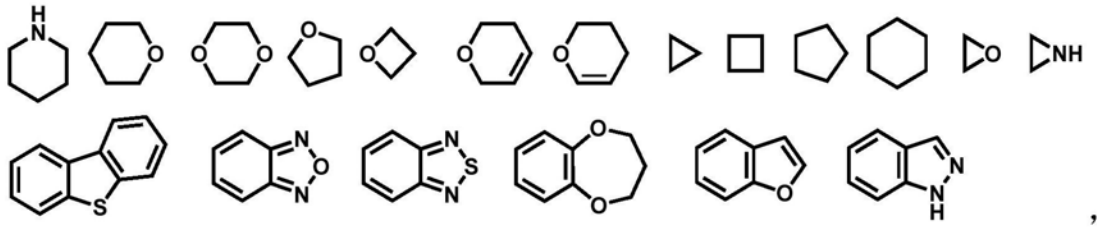
[0096] 

[0097] 其中Y_1、R_1和R_2如先前所定义。优选地，R_1是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基；并且R_2是任选取代的芳基或任选取代的杂芳基，或R_2是任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基。

[0098] 在某些实施方式中，本发明涉及式(V-1)～式(V-8)的化合物，及其药学上可接受的盐，其中R_1和R_2衍生自去掉氢原子的以下中的一种：

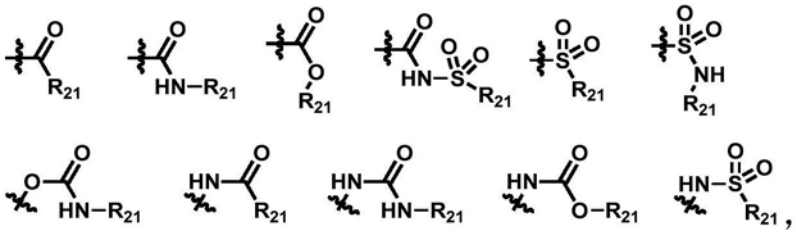


[0099]  ，或

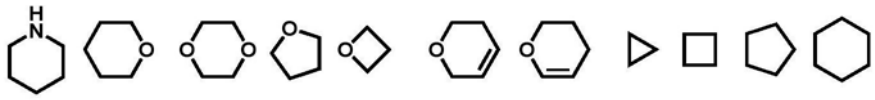
 ，

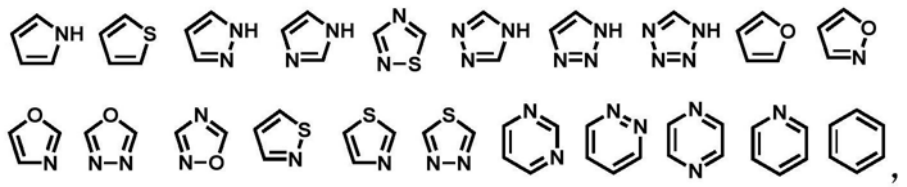
[0100] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

[0101] 在某些实施方式中，本发明涉及式(V-1)～式(V-8)的化合物，及其药学上可接受的盐，其中R_1和R_2选自以下中的一种：

[0102] 

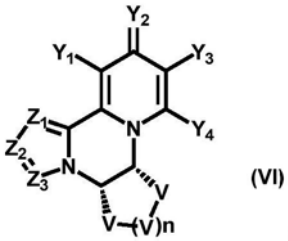
[0103] 其中每个R_{21}独立地选自-CH_3、-异丙基、-叔丁基或去掉氢原子的以下中的一种：



[0104] 

[0105] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

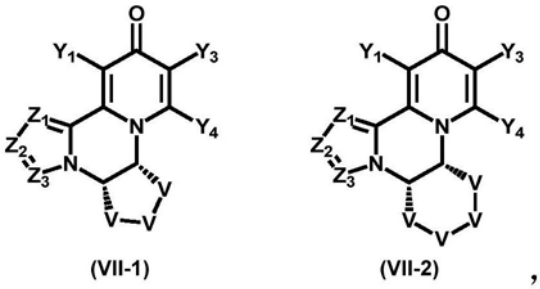
[0106] 在另一种实施方式中，式(I)的化合物由式(VI)或其药学上可接受的盐表示：

[0107] 

(VI)

[0108] 其中Y_1、Y_2、Y_3、Y_4、Z_1、Z_2和Z_3如先前所定义，一个V是-O-、-C(O)-、-S-、-$S(O)_2$-、-NR_{22}-或-$C(R_{22})_2$-，并且其他V独立地是-O-、-NR_{22}-或-$C(R_{22})_2$-；每个R_{22}独立地是氢、任选取代的-C_1-C_6烷基、任选取代的-C_2-C_6烯基、任选取代的-C_2-C_6炔基、任选取代的C_1-C_6烷氧基；任选取代的-C_3-C_7环烷基、任选取代的3-至7-元杂环、任选取代的芳基或任选取代的杂芳基；n是0、1、2或3。在某些实施方式中，两个相邻的V是-$C(R_{22})_2$-。替代地，两个相邻的V一起形成-$C(R_{22})$=$C(R_{22})$-。

[0109] 在另一种实施方式中，式(I)的化合物由式(VII-1)或式(VII-2)或其药学上可接受的盐表示：

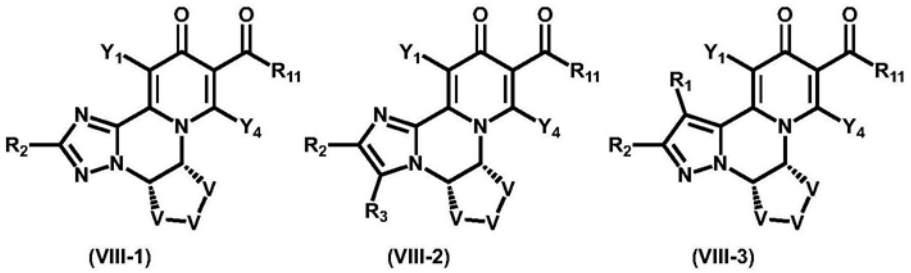
[0110] 

(VII-1) (VII-2)

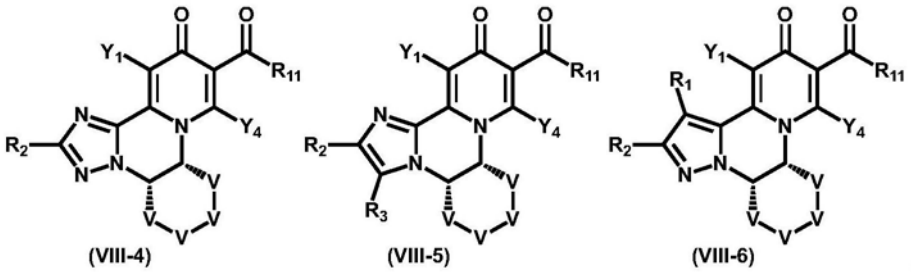
[0111] 其中Y_1、Y_3、Y_4、Z_1、Z_2、Z_3和V如先前所定义。替代地，两个相邻的V一起形成-$C(R_{22})$=$C(R_{22})$-，R_{22}如先前所定义。

[0112] 在另一种实施方式中，式(I)的化合物由式(VIII-1)～(VIII-6)中的一个或其药

学上可接受的盐表示：



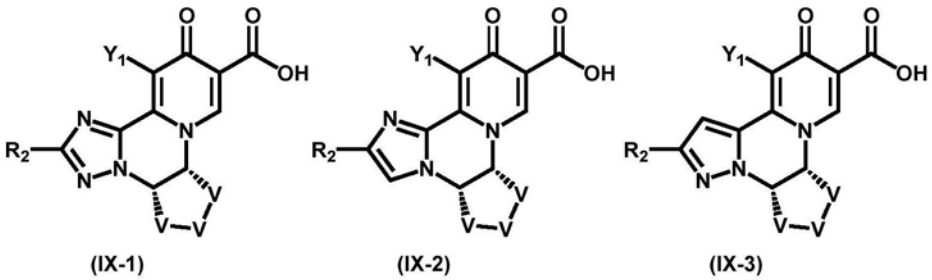
[0113]



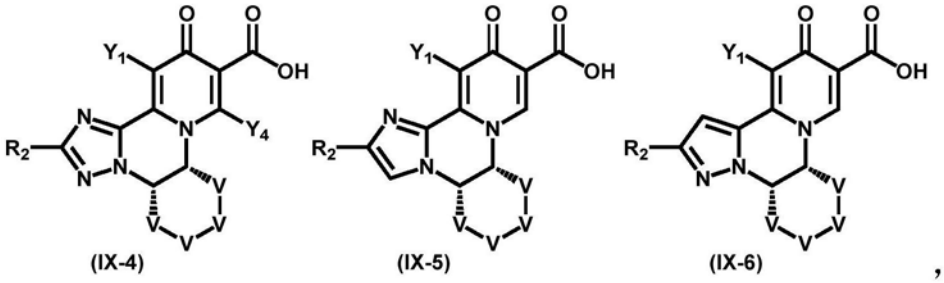
，

[0114] 其中Y_1、Y_4、R_1、R_2、R_3、R_{11}和V如先前所定义。

[0115] 在另一种实施方式中，式(I)的化合物由式(IX-1)～(IX-6)中的一个或其药学上可接受的盐表示：



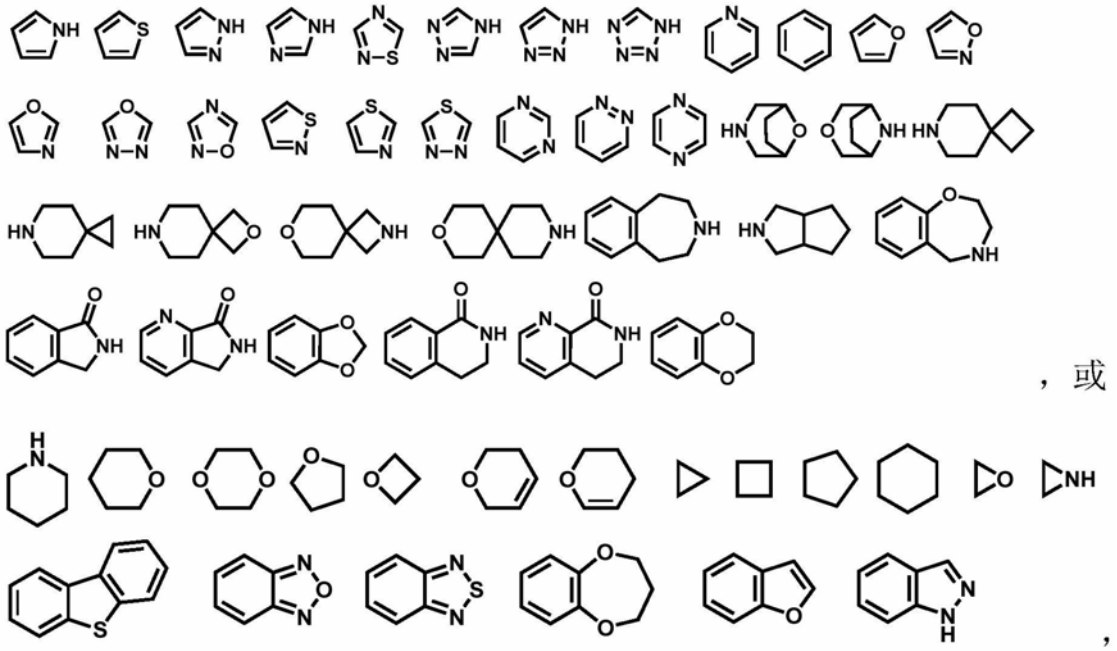
[0116]



，

[0117] 其中Y_1、R_2和V如先前所定义。优选地，R_2是任选取代的芳基或任选取代的杂芳基，或R_2是任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基。

[0118] 在另一种实施方式中，化合物由式(IX-1)～(IX-6)中的一个或其药学上可接受的盐表示，其中R_2衍生自去掉氢原子的以下中的一种：

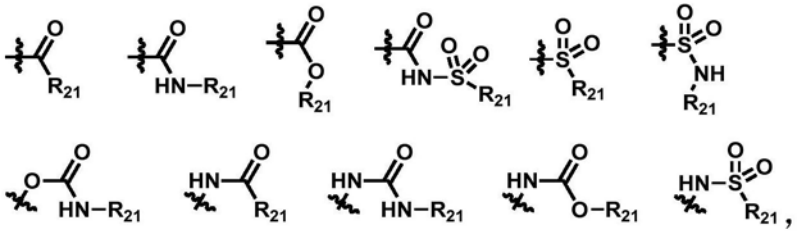
[0119] 

，或

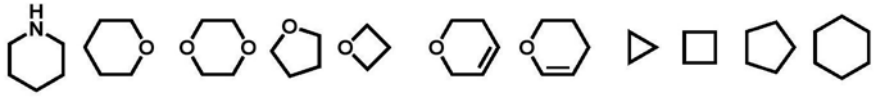
，

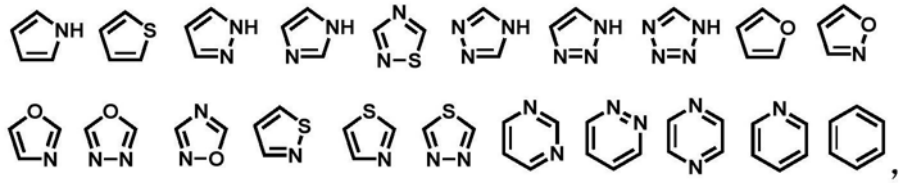
[0120] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

[0121] 在另一种实施方式中，化合物由式(IX-1)～(IX-6)中的一个或其药学上可接受的盐表示，其中R_2独立地选自以下中的一种：

[0122] 

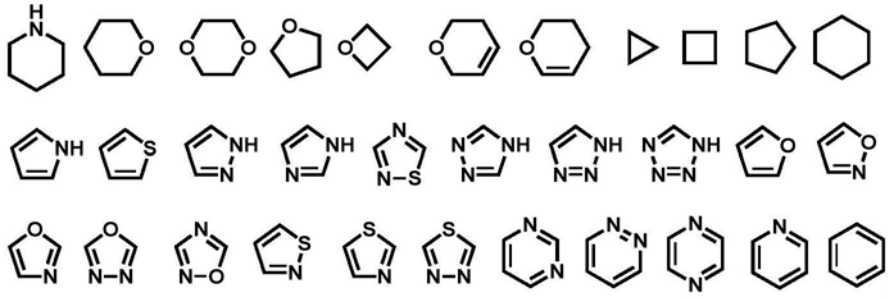
[0123] 其中每个R_{21}独立地选自-CH_3、-异丙基、-叔丁基或去掉氢原子的以下中的一种：



[0124] 

[0125] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

[0126] 在另一种实施方式中，化合物由式(V-1)、式(V-5)、式(IX-1)或式(IX-4)或其药学上可接受的盐表示，其中R_2选自卤素、-CN、-CH_3、-CF_3、-CHF_2、-C(O)CH_3、-OCH_3、-OCF_3、-$OCHF_2$、-OH、-OR_{11}、-NH_2和-NHR_{12}，其中R_{11}和R_{12}各自独立地选自去掉氢原子的以下中的一种：

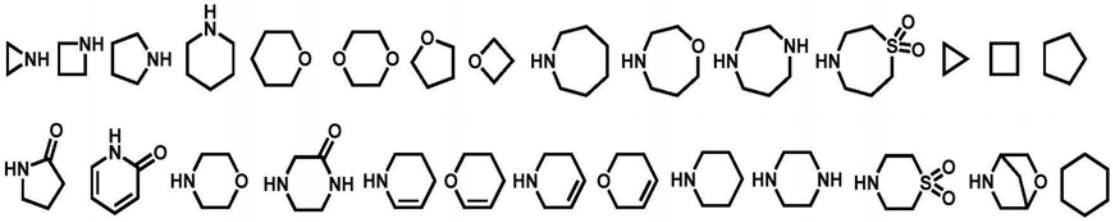


[0127]

[0128] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

[0129] 在另一种实施方式中，化合物由式(V-1)、式(V-5)、式(IX-1)或式(IX-4)或其药学上可接受的盐表示，其中R_2衍生自去掉氢原子的以下中的一种：

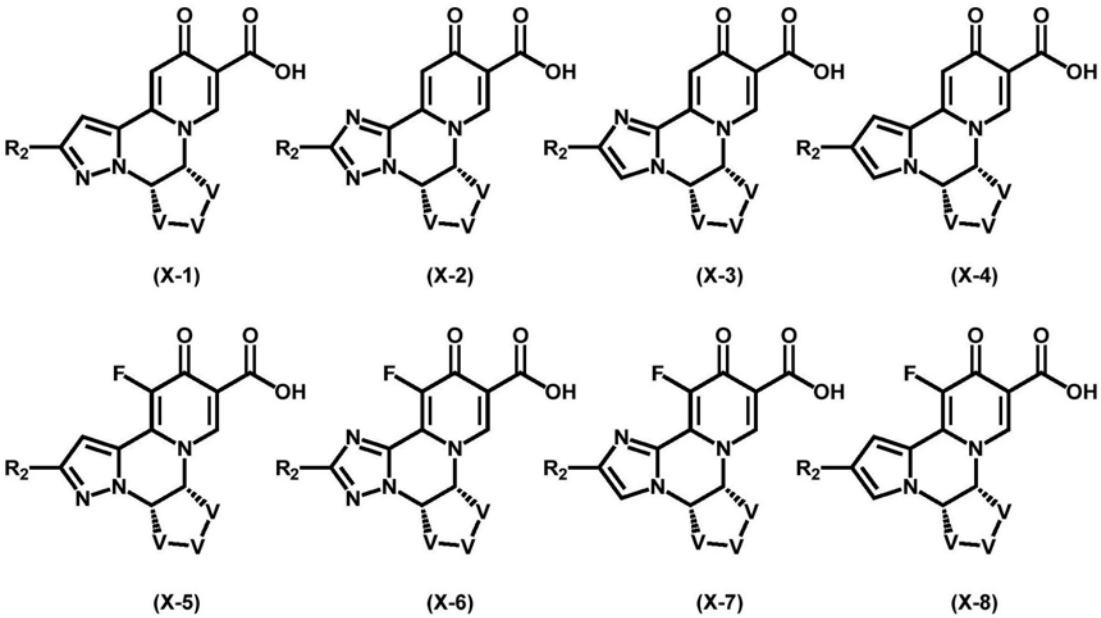
[0130]



[0131] 其中这些基团中的每个被选自卤素、CN、-OR_{11}、-$NR_{11}R_{12}$、任选取代的C_1-C_6烷基以及任选取代的3-至8-元杂环的一至四个基团任选地取代。

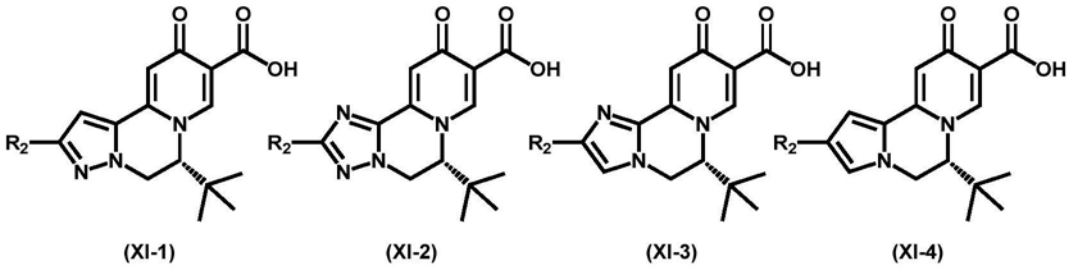
[0132] 在另一种实施方式中，式(I)的化合物由式(X-1)～(X-8)中的一个或其药学上可接受的盐表示：

[0133]



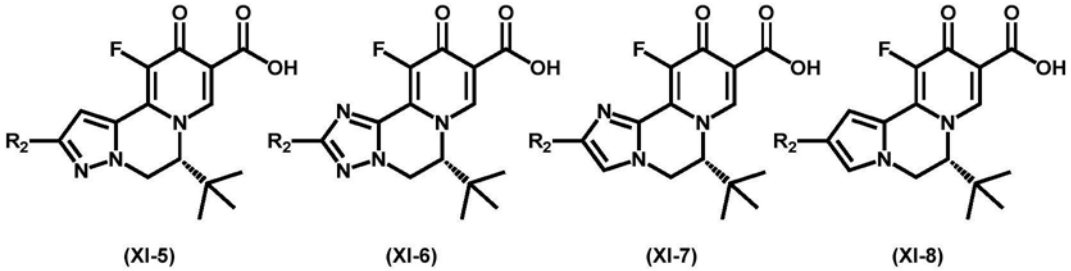
[0134] 其中R_2和V如先前所定义。优选地，R_2是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基。

[0135] 在另一种实施方式中，式(I)的化合物由式(XI-1)～(XI-8)中的一个或其药学上可接受的盐表示：



(XI-1) (XI-2) (XI-3) (XI-4)

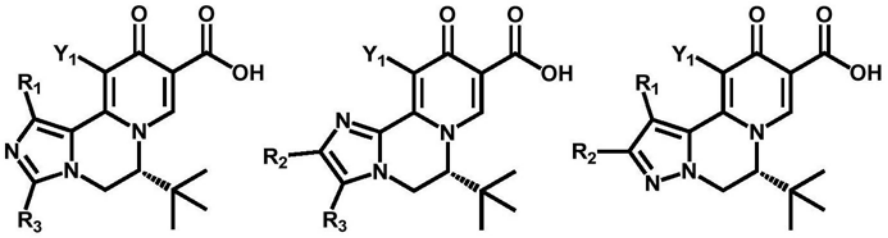
[0136]



(XI-5) (XI-6) (XI-7) (XI-8) ,

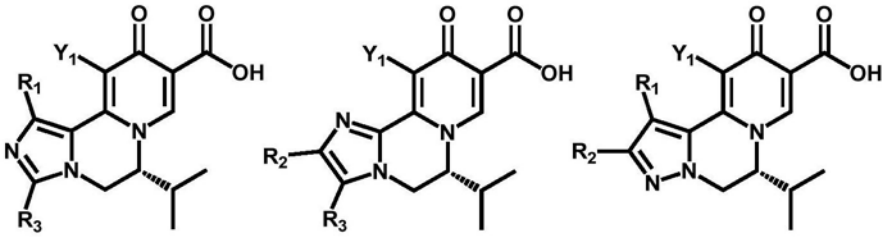
[0137] 其中R_2如先前所定义。优选地,R_2是任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基或任选取代的3-至8-元杂环烷基。

[0138] 在另一种实施方式中,式(I)的化合物由式(XII-1)～(XII-6)中的一个或其药学上可接受的盐表示:



(XII-1) (XII-2) (XII-3)

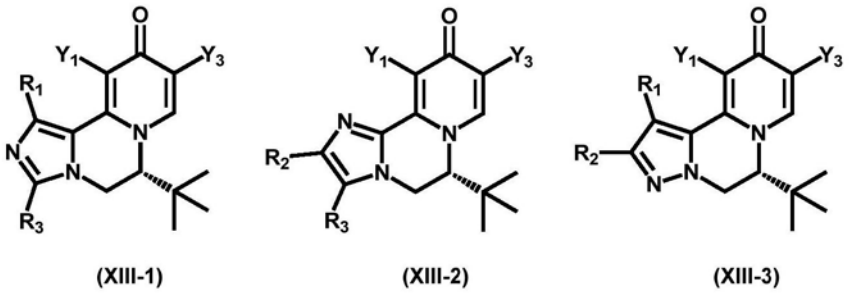
[0139]



(XII-4) (XII-5) (XII-6) ,

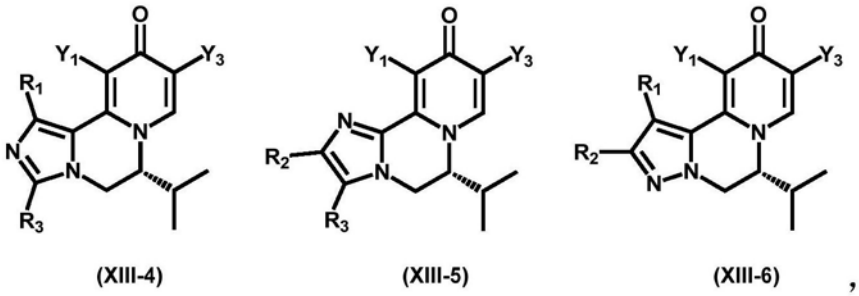
[0140] 其中Y_1、R_1、R_2和R_3如先前所定义。优选地,Y_1是H或F;R_1、R_2和R_3各自独立地选自氢、卤素、任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基以及任选取代的3-至8-元杂环烷基。更优选地,Y_1是H;并且R_1、R_2和R_3各自独立地选自任选取代的芳基以及任选取代的杂芳基。

[0141] 在另一种实施方式中,式(I)的化合物由式(XIII-1)～(XIII-6)中的一个或其药学上可接受的盐表示:



(XIII-1) (XIII-2) (XIII-3)

[0142]

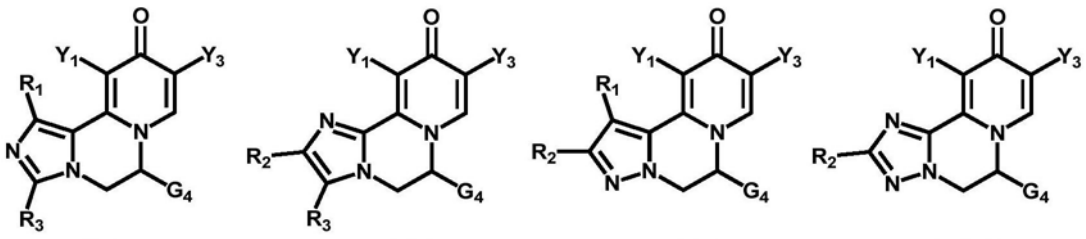


(XIII-4) (XIII-5) (XIII-6) ,

[0143] 其中Y_1、Y_3、R_1、R_2和R_3如先前所定义。优选地，Y_1是H或F；Y_3是-COOH或三唑基；R_1、R_2和R_3各自独立地选自氢、卤素、任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基以及任选取代的3-至8-元杂环烷基。更优选地，Y_1是H；Y_3是-COOH，并且R_1、R_2和R_3各自独立地选自任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基以及任选取代的3-至8-元杂环烷基。

[0144] 在另一种实施方式中，式(I)的化合物由式(XIV-1)(XIV-4)中的一个或其药学上可接受的盐表示：

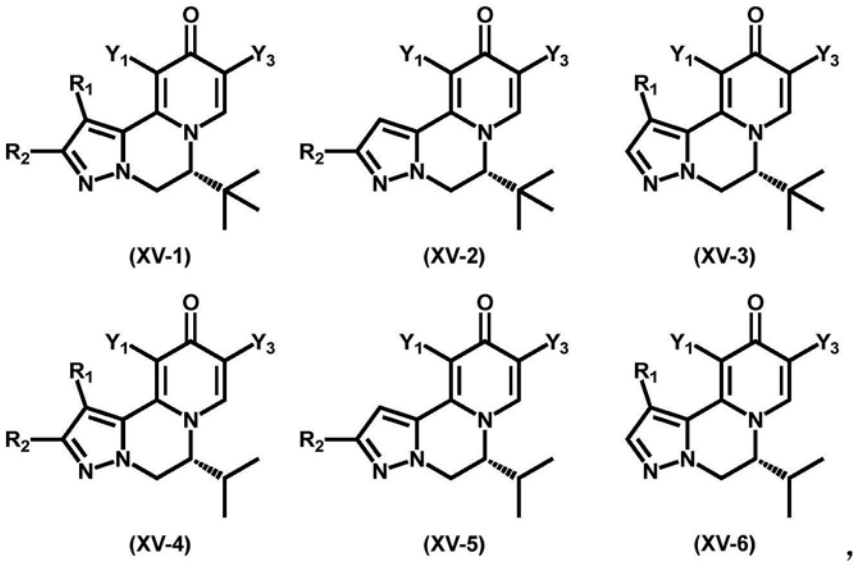
[0145]



(XIV-1) (XIV-2) (XIV-3) (XIV-4) ,

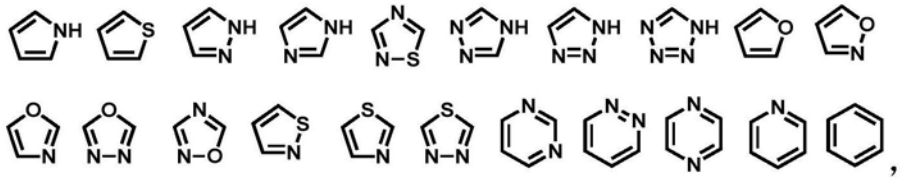
[0146] 其中Y_1、Y_3、R_1、R_2、R_3和G_4如先前所定义。优选地，Y_1是H或F；Y_3是-COOH或三唑基；G_4是叔丁基或异丙基；R_1、R_2和R_3各自独立地选自氢、卤素、任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基以及任选取代的3-至8-元杂环烷基。更优选地，Y_1是H；Y_3是-COOH或三唑基；G_4是叔丁基或异丙基；并且R_1、R_2和R_3各自独立地选自任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基以及任选取代的3-至8-元杂环烷基。

[0147] 在另一种实施方式中，式(I)的化合物由式(XV-1)～(XV-6)中的一个或其药学上可接受的盐表示：

[0148] 

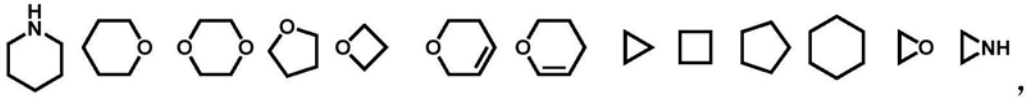
[0149] 其中Y_1、Y_3、R_1和R_2如先前所定义。优选地，Y_1是H或F；Y_3是-COOH或三唑基；R_1和R_2各自独立地选自任选取代的芳基、任选取代的芳基烷基、任选取代的杂芳基、任选取代的杂芳基烷基、任选取代的-C_3-C_8环烷基以及任选取代的3-至8-元杂环烷基。更优选地，Y_1是H；Y_3是-COOH或三唑基；并且R_1和R_2各自独立地选自任选取代的芳基、任选取代的杂芳基、任选取代的-C_3-C_8环烷基以及任选取代的3-至8-元杂环烷基。

[0150] 在另一种实施方式中，化合物由式(XII-1)～式(XII-6)或式(XIII-1)～式(XIII-6)或式(XIV-1)～式(XIV-4)或式(XV-1)～式(XV-6)或其药学上可接受的盐表示，其中R_1、R_2和R_3各自独立地选自去掉氢原子的以下中的一种：

[0151] 

[0152] 其中这些基团中的每个被任选地取代。

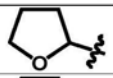
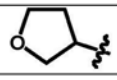
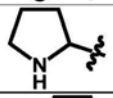
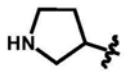
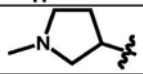
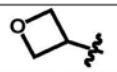
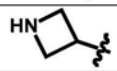
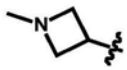
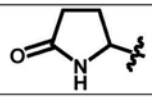
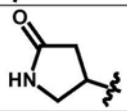
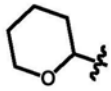
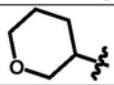
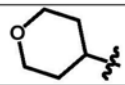
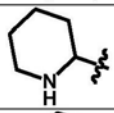
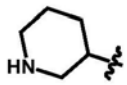
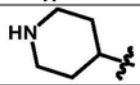
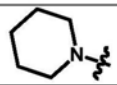
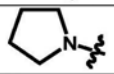
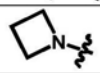
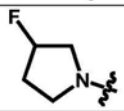
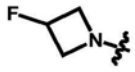
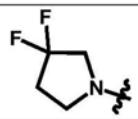
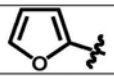
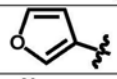
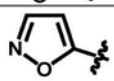
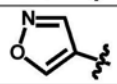
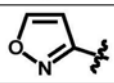
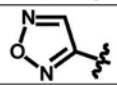
[0153] 在另一种实施方式中，化合物由式(XII-1)～式(XII-6)或式(XIII-1)～式(XIII-6)或式(XIV-1)～式(XIV-4)或式(XV-1)～式(XV-6)或其药学上可接受的盐表示，其中R_1、R_2和R_3各自独立地选自去掉氢原子的以下中的一种：

[0154] 

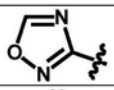
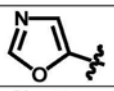
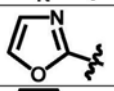
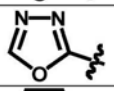
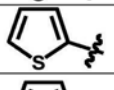
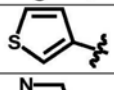
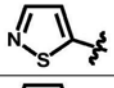
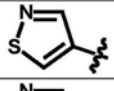
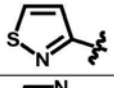
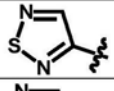
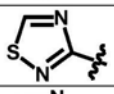
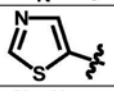
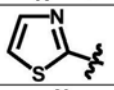
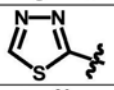
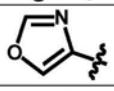
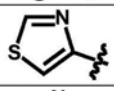
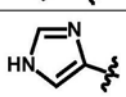
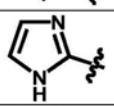
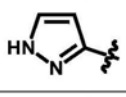
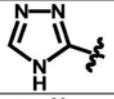
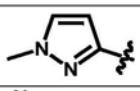
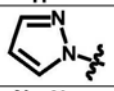
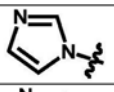
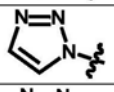
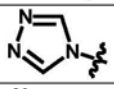
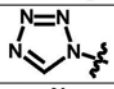
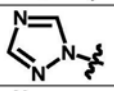
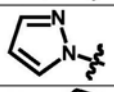
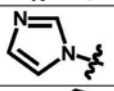
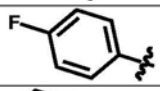
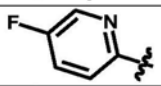
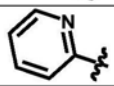
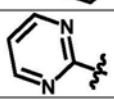
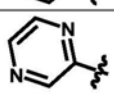
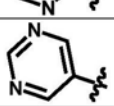
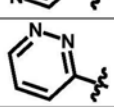
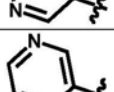
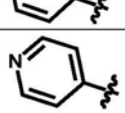
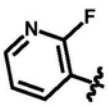
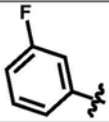
[0155] 其中这些基团中的每个被任选地取代。

[0156] 在另一种实施方式中，本发明的化合物由式(XII-1)～式(XII-6)或式(XIII-1)～式(XIII-6)或式(XIV-1)～(XIV-4)或式(XV-1)～式(XV-6)或其药学上可接受的盐表示，其中R_1、R_2和R_3中的至少一个独立地选自在下表中的基团。

[0157]

条目	R_1、R_2或R_3	条目	R_1、R_2或R_3
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	
31		32	

[0158]

33		34	
35		36	
37		38	
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	
55		56	
57		58	
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	

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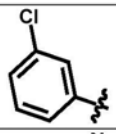
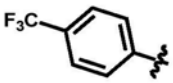
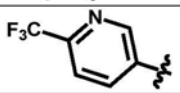
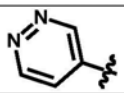
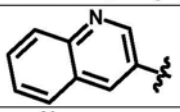
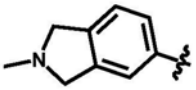
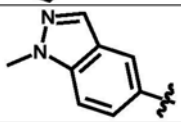
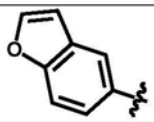
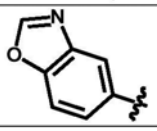
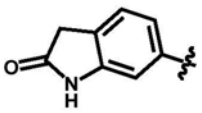
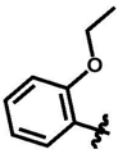
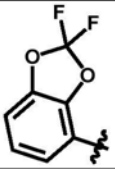
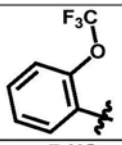
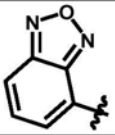
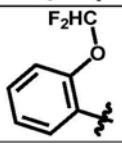
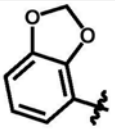
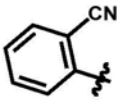
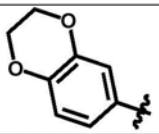
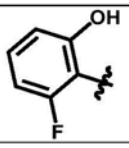
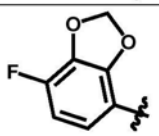
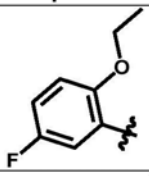
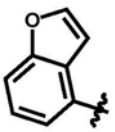
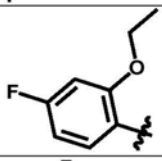
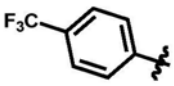
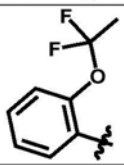
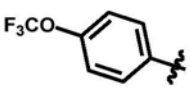
73		74	
75		76	
77		78	
79		80	
81		82	
83		84	
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	
97		98	

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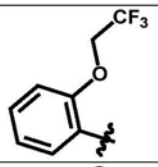
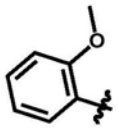
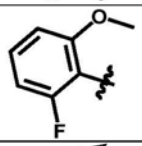
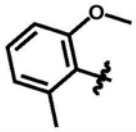
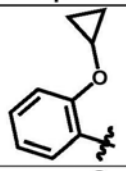
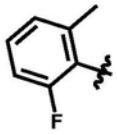
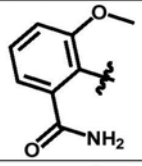
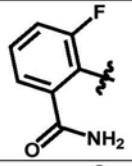
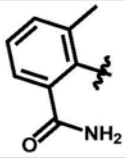
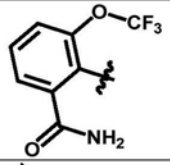
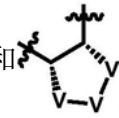
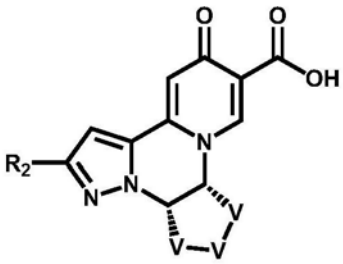
99		100	
101		102	
103		104	
105		106	
107		108	
109		110	

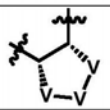
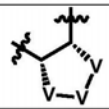
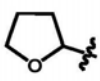
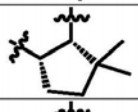
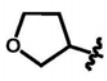
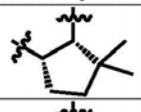
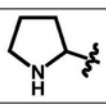
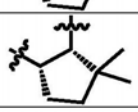
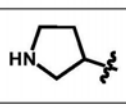
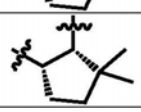
[0161] 本发明的代表性化合物包括但不限于根据式(X-1)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2和  在表1中定义。

[0162] 

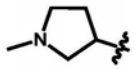
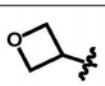
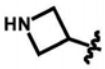
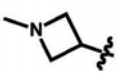
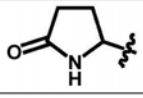
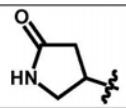
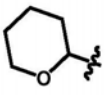
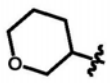
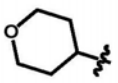
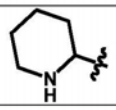
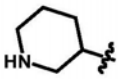
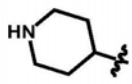
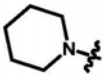
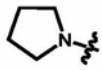
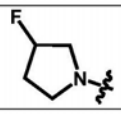
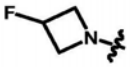
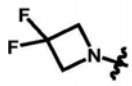
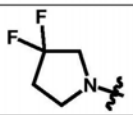
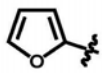
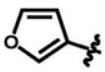
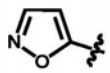
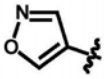
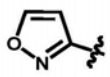
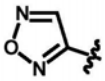
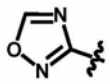
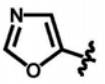
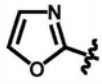
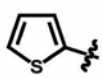
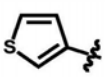
(X-1)

[0163] 表1

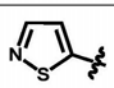
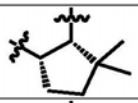
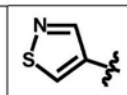
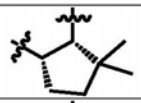
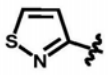
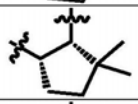
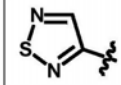
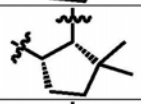
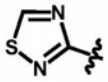
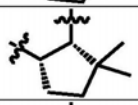
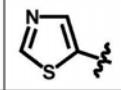
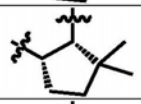
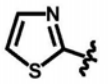
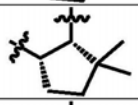
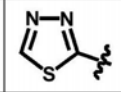
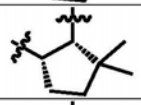
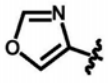
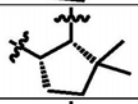
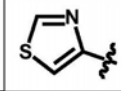
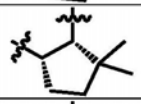
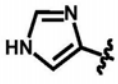
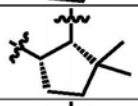
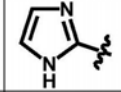
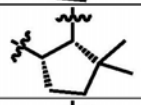
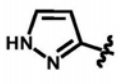
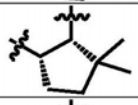
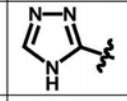
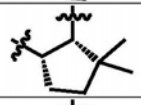
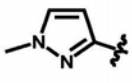
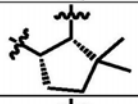
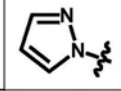
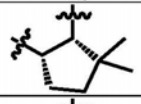
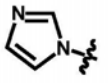
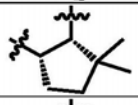
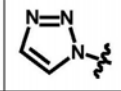
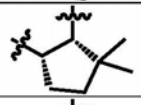
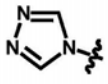
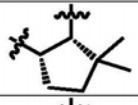
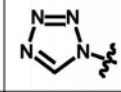
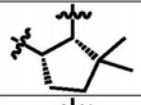
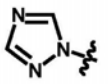
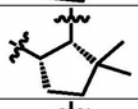
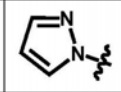
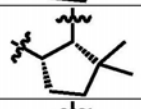
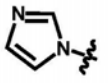
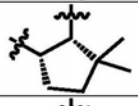
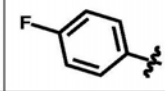
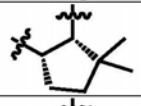
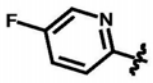
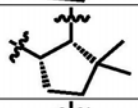
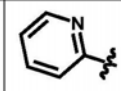
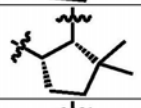
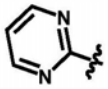
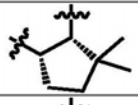
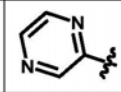
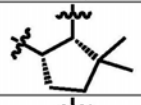
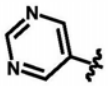
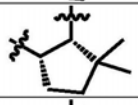
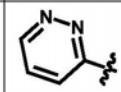
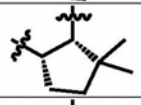
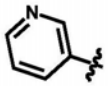
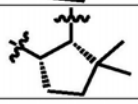
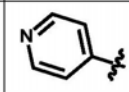
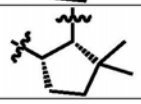
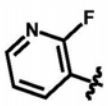
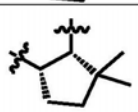
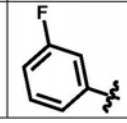
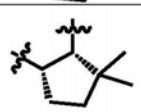
[0164]

化合物	R_2		化合物	R_2	
1-1			1-2		
1-3			1-4		

[0165]

1-5			1-6		
1-7			1-8		
1-9			1-10		
1-11			1-12		
1-13			1-14		
1-15			1-16		
1-17			1-18		
1-19			1-20		
1-21			1-22		
1-23			1-24		
1-25			1-26		
1-27			1-28		
1-29			1-30		
1-31			1-32		
1-33			1-34		
1-35			1-36		
1-37			1-38		

[0166]

1-39			1-40		
1-41			1-42		
1-43			1-44		
1-45			1-46		
1-47			1-48		
1-49			1-50		
1-51			1-52		
1-53			1-54		
1-55			1-56		
1-57			1-58		
1-59			1-60		
1-61			1-62		
1-63			1-64		
1-65			1-66		
1-67			1-68		
1-69			1-70		
1-71			1-72		

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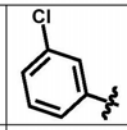
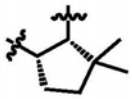
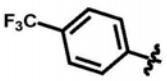
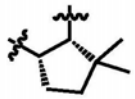
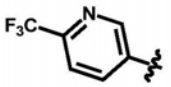
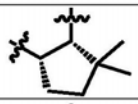
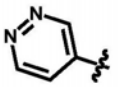
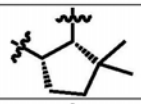
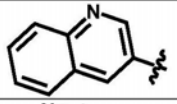
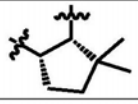
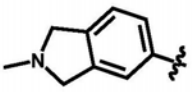
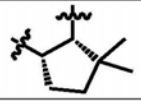
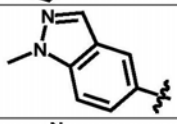
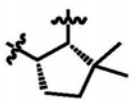
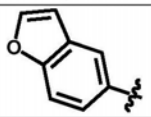
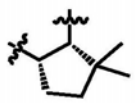
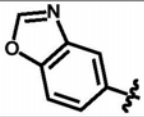
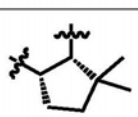
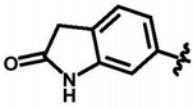
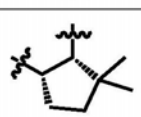
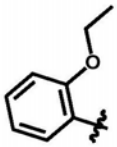
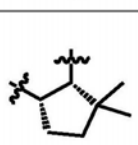
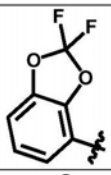
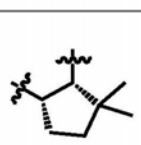
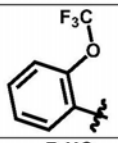
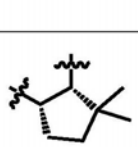
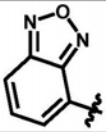
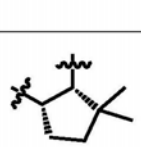
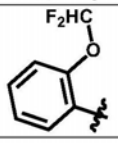
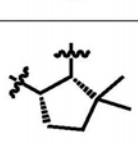
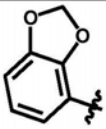
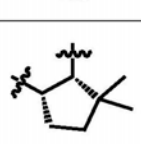
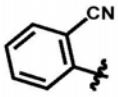
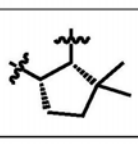
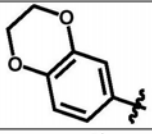
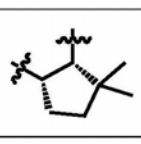
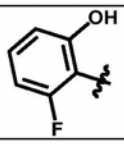
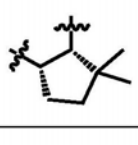
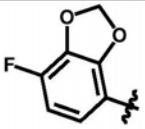
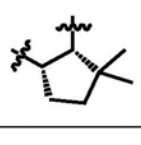
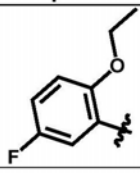
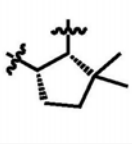
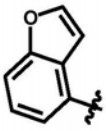
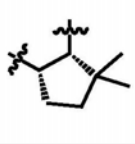
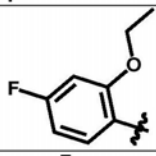
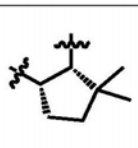
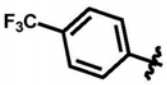
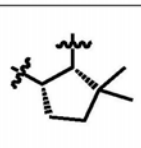
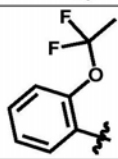
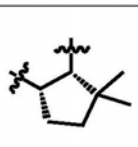
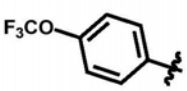
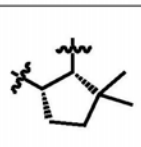
1-73			1-74		
1-75			1-76		
1-77			1-78		
1-79			1-80		
1-81			1-82		
1-83			1-84		
1-85			1-86		
1-87			1-88		
1-89			1-90		
1-91			1-92		
1-93			1-94		
1-95			1-96		
1-97			1-98		

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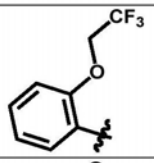
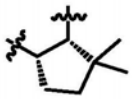
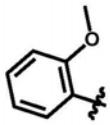
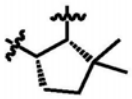
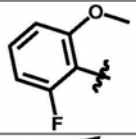
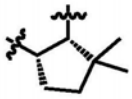
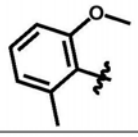
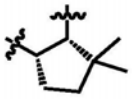
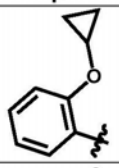
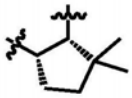
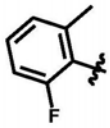
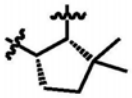
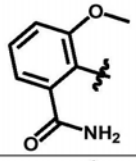
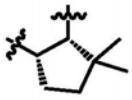
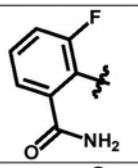
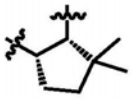
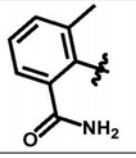
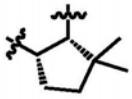
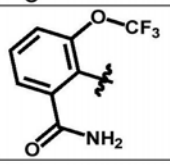
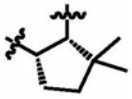
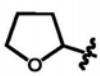
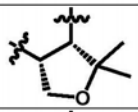
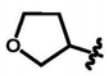
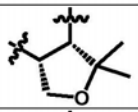
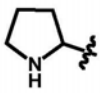
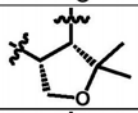
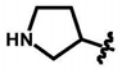
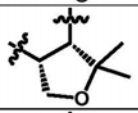
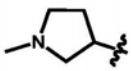
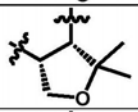
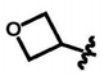
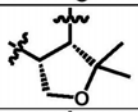
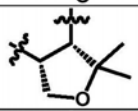
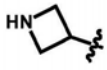
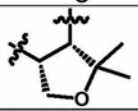
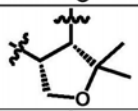
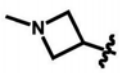
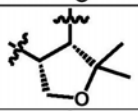
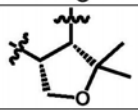
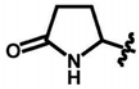
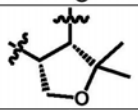
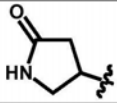
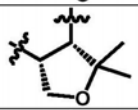
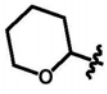
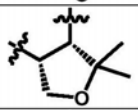
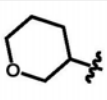
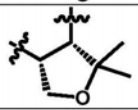
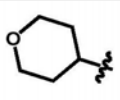
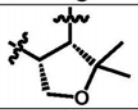
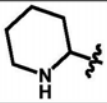
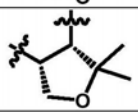
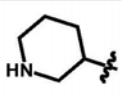
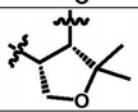
1-99			1-100		
1-101			1-102		
1-103			1-104		
1-105			1-106		
1-107			1-108		
1-109			1-110		
1-111			1-112		
1-113			1-114		
1-115			1-116		
1-117			1-118		
1-119			1-120		
1-121			1-122		
1-123			1-124		
1-125			1-126		

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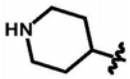
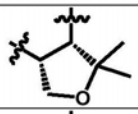
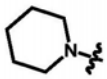
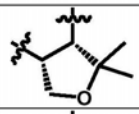
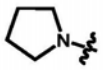
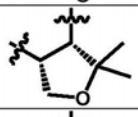
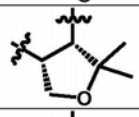
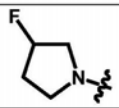
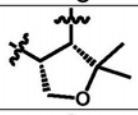
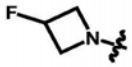
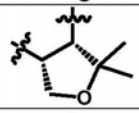
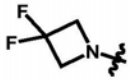
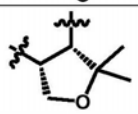
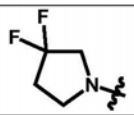
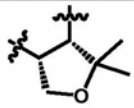
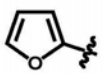
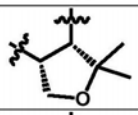
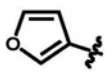
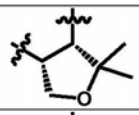
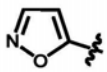
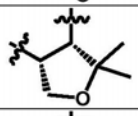
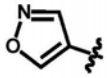
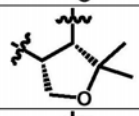
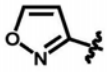
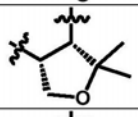
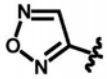
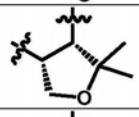
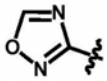
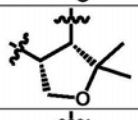
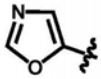
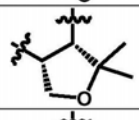
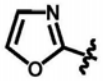
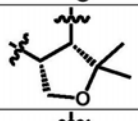
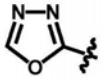
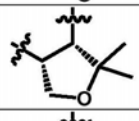
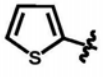
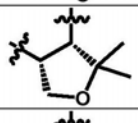
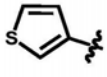
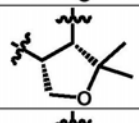
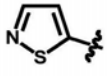
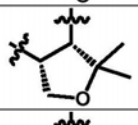
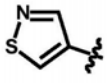
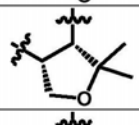
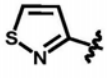
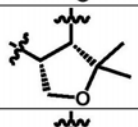
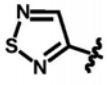
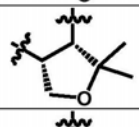
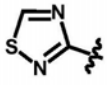
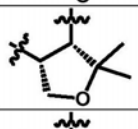
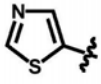
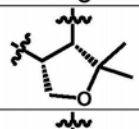
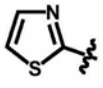
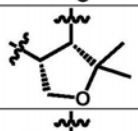
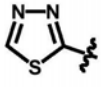
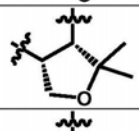
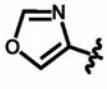
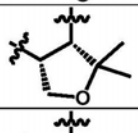
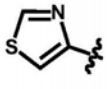
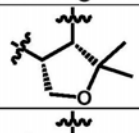
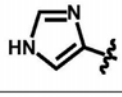
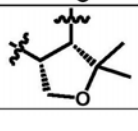
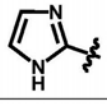
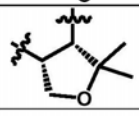
1-127			1-128		
1-129			1-130		
1-131			1-132		
1-133			1-134		
1-135			1-136		
1-137			1-138		
1-139			1-140		
1-141			1-142		
1-143			1-144		
1-145			1-146		
1-147			1-148		
1-149			1-150		
1-151			1-152		
1-153			1-154		
1-155			1-156		
1-157			1-158		

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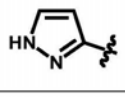
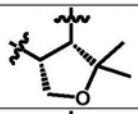
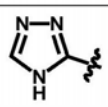
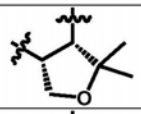
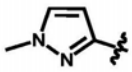
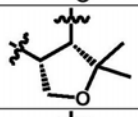
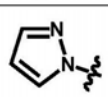
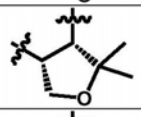
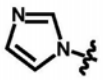
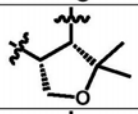
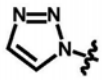
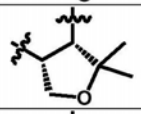
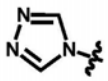
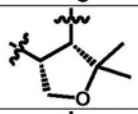
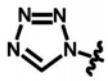
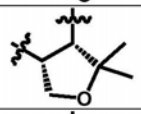
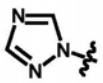
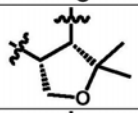
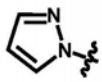
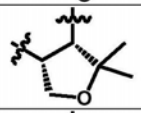
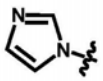
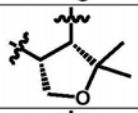
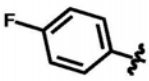
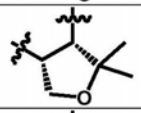
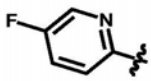
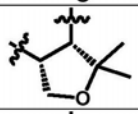
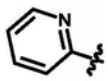
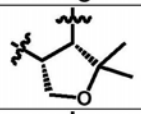
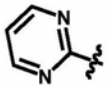
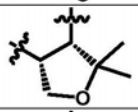
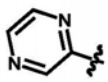
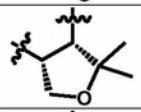
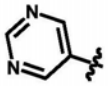
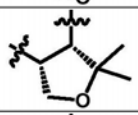
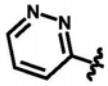
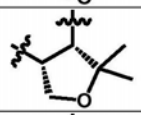
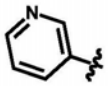
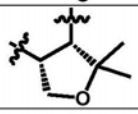
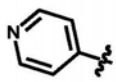
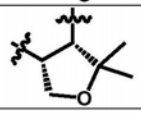
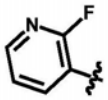
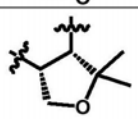
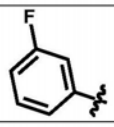
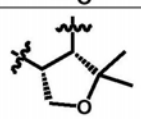
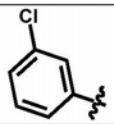
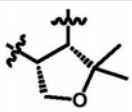
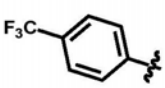
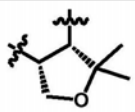
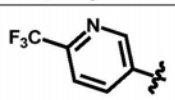
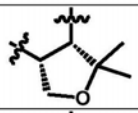
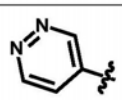
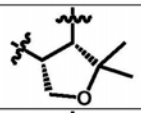
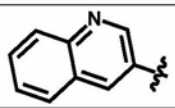
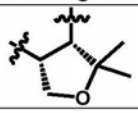
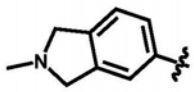
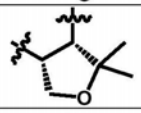
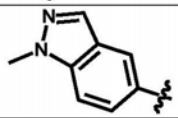
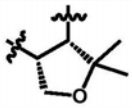
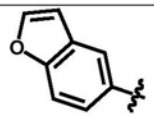
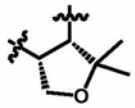
1-159			1-160		
1-161			1-162		
1-163			1-164		
1-165			1-166		
1-167			1-168		
1-169			1-170		
1-171			1-172		
1-173			1-174		
1-175			1-176		
1-177			1-178		
1-179			1-180		
1-181			1-182		
1-183			1-184		
1-185			1-186		
1-187			1-188		

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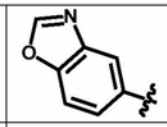
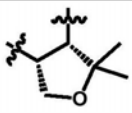
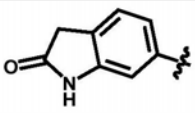
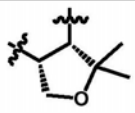
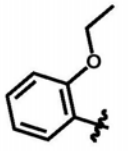
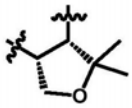
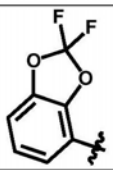
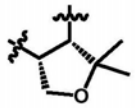
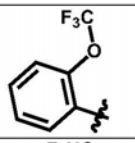
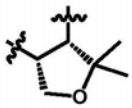
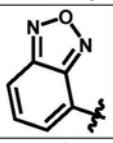
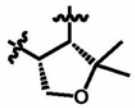
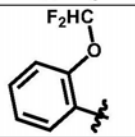
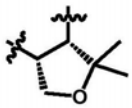
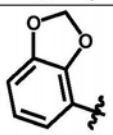
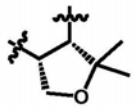
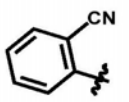
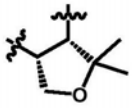
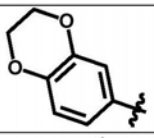
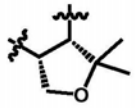
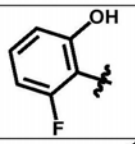
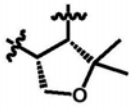
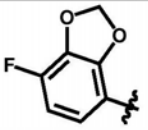
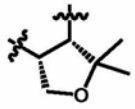
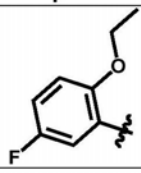
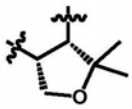
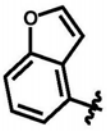
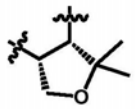
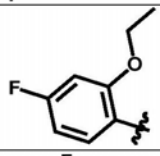
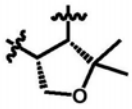
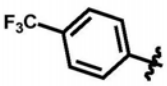
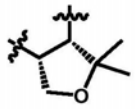
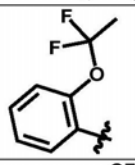
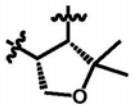
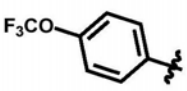
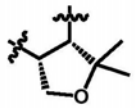
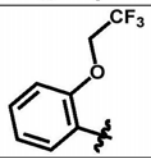
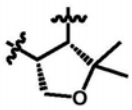
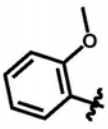
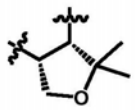
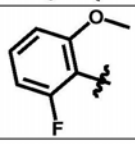
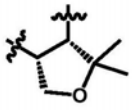
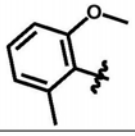
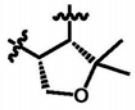
1-189			1-190		
1-191			1-192		
1-193			1-194		
1-195			1-196		
1-197			1-198		
1-199			1-200		
1-201			1-202		
1-203			1-204		
1-205			1-206		
1-207			1-208		
1-209			1-210		

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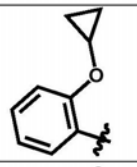
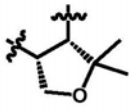
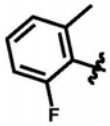
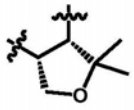
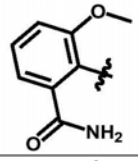
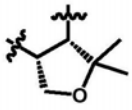
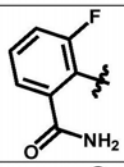
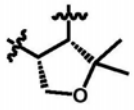
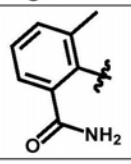
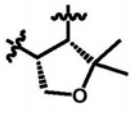
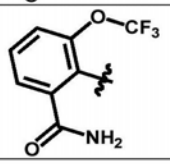
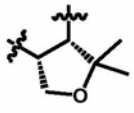
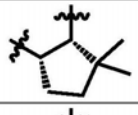
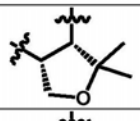
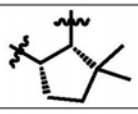
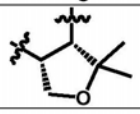
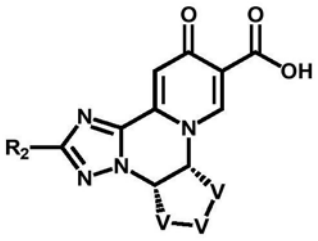
1-211			1-212		
1-213			1-214		
1-215			1-216		
1-217			1-218		
1-219			1-220		

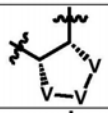
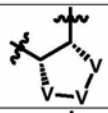
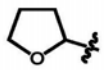
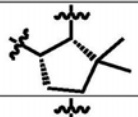
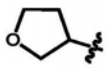
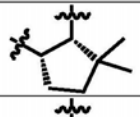
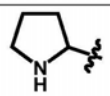
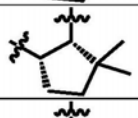
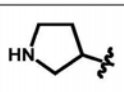
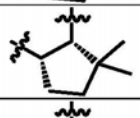
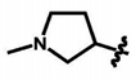
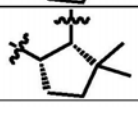
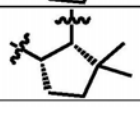
[0173] 本发明的代表性化合物包括但不限于根据式(X-2)的化合物，及其药学上可接受的盐，其中每一种化合物的R_2和 在表2中定义。

[0174] 

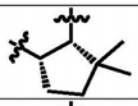
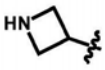
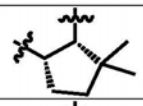
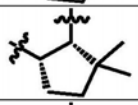
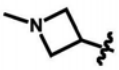
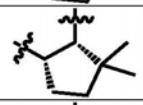
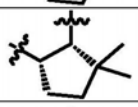
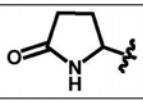
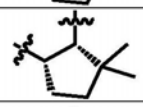
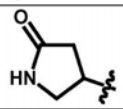
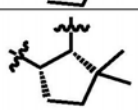
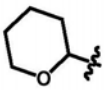
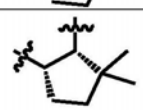
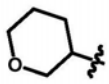
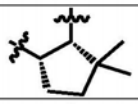
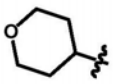
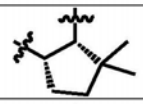
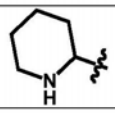
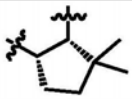
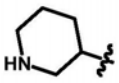
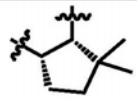
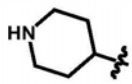
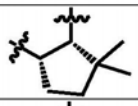
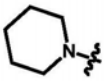
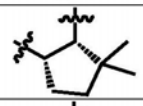
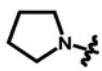
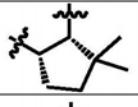
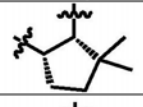
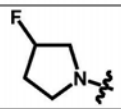
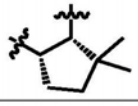
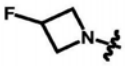
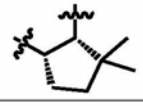
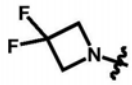
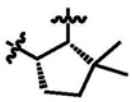
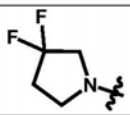
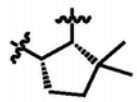
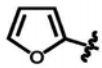
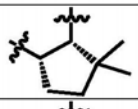
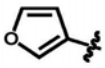
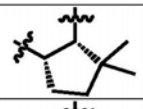
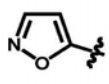
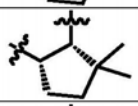
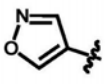
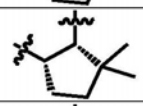
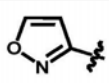
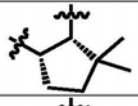
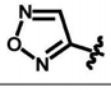
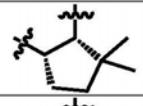
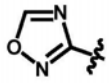
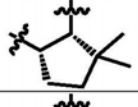
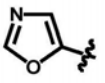
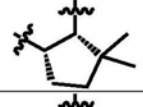
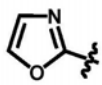
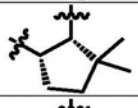
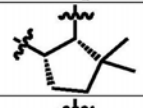
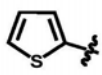
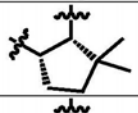
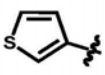
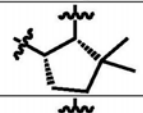
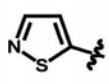
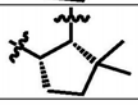
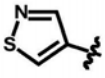
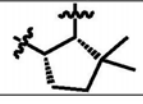
(X-2)

[0175] 表2

[0176]

化合物	R_2		化合物	R_2	
2-1			2-2		
2-3			2-4		
2-5			2-6		

[0177]

2-7			2-8		
2-9			2-10		
2-11			2-12		
2-13			2-14		
2-15			2-16		
2-17			2-18		
2-19			2-20		
2-21			2-22		
2-23			2-24		
2-25			2-26		
2-27			2-28		
2-29			2-30		
2-31			2-32		
2-33			2-34		
2-35			2-36		
2-37			2-38		
2-39			2-40		

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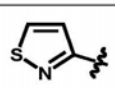
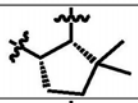
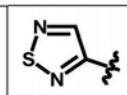
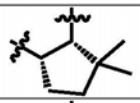
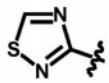
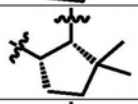
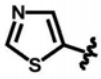
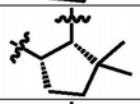
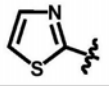
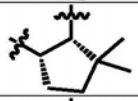
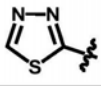
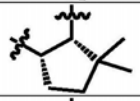
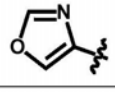
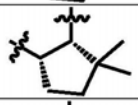
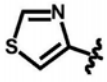
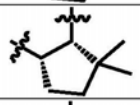
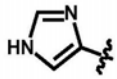
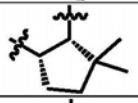
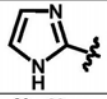
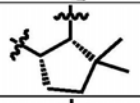
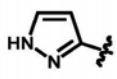
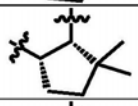
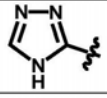
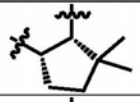
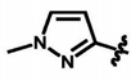
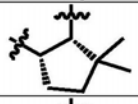
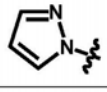
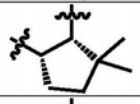
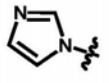
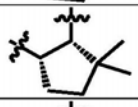
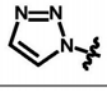
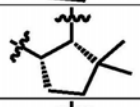
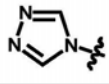
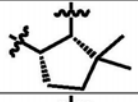
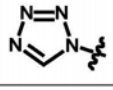
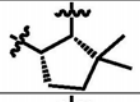
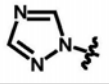
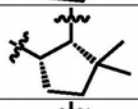
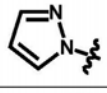
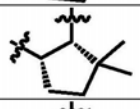
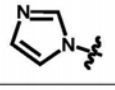
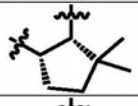
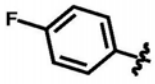
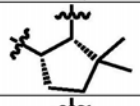
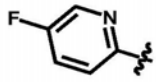
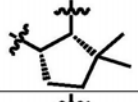
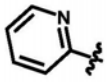
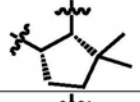
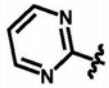
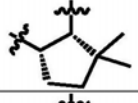
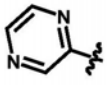
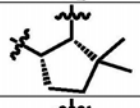
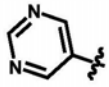
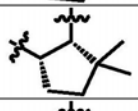
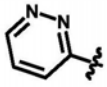
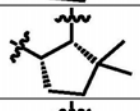
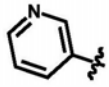
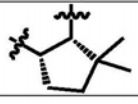
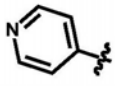
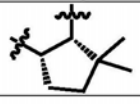
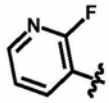
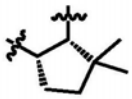
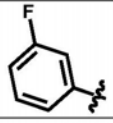
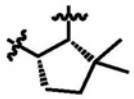
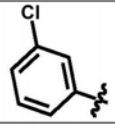
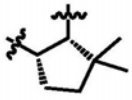
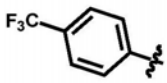
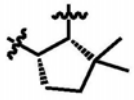
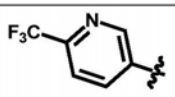
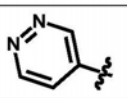
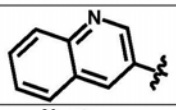
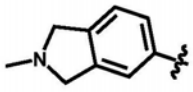
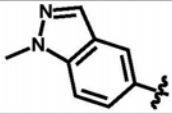
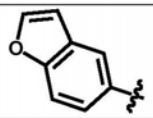
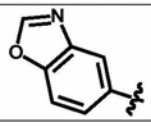
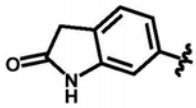
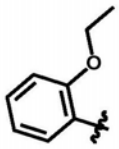
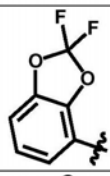
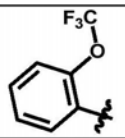
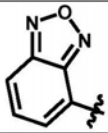
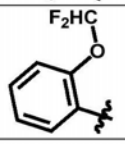
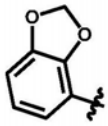
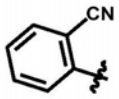
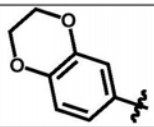
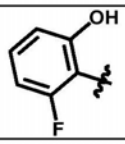
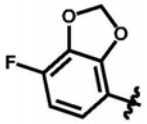
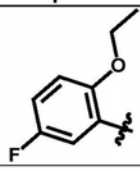
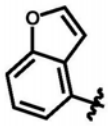
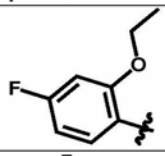
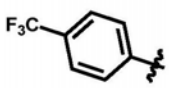
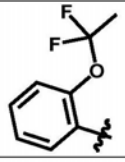
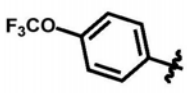
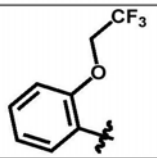
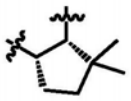
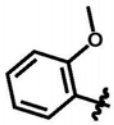
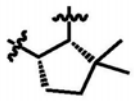
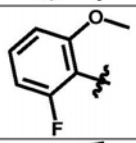
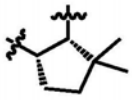
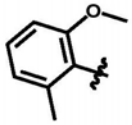
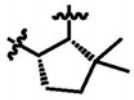
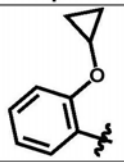
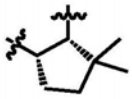
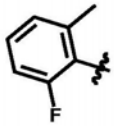
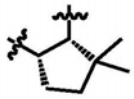
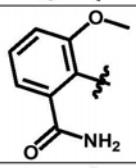
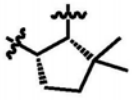
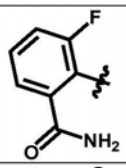
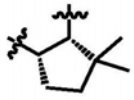
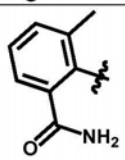
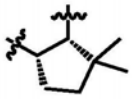
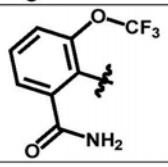
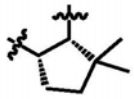
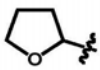
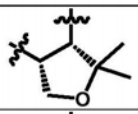
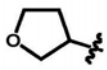
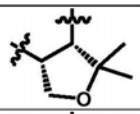
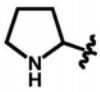
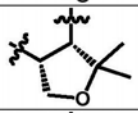
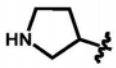
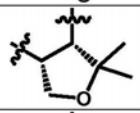
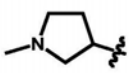
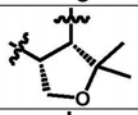
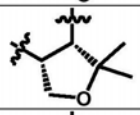
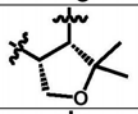
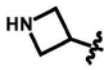
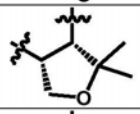
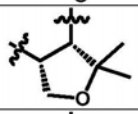
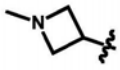
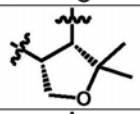
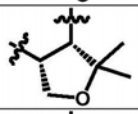
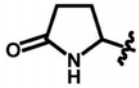
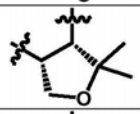
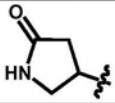
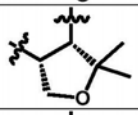
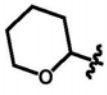
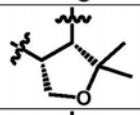
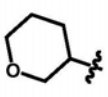
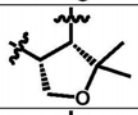
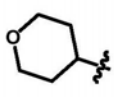
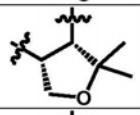
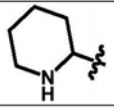
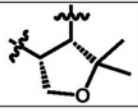
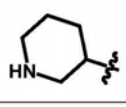
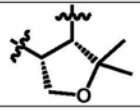
2-41			2-42		
2-43			2-44		
2-45			2-46		
2-47			2-48		
2-49			2-50		
2-51			2-52		
2-53			2-54		
2-55			2-56		
2-57			2-58		
2-59			2-60		
2-61			2-62		
2-63			2-64		
2-65			2-66		
2-67			2-68		
2-69			2-70		
2-71			2-72		
2-73			2-74		

[0179]

2-75			2-76		
2-77			2-78		
2-79			2-80		
2-81			2-82		
2-83			2-84		
2-85			2-86		
2-87			2-88		
2-89			2-90		
2-91			2-92		
2-93			2-94		
2-95			2-96		
2-97			2-98		

[0180]

2-99			2-100		
2-101			2-102		
2-103			2-104		
2-105			2-106		
2-107			2-108		
2-109			2-110		
2-111			2-112		
2-113			2-114		
2-115			2-116		
2-117			2-118		
2-119			2-120		
2-121			2-122		
2-123			2-124		
2-125			2-126		

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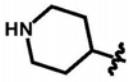
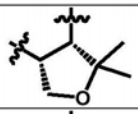
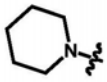
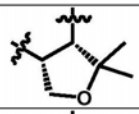
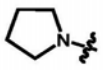
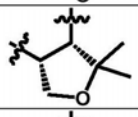
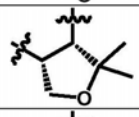
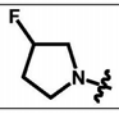
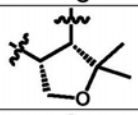
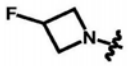
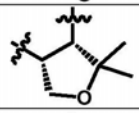
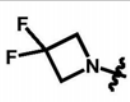
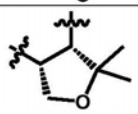
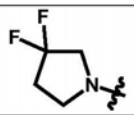
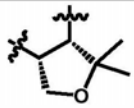
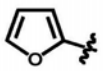
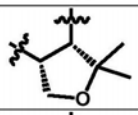
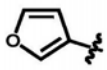
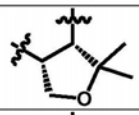
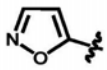
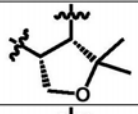
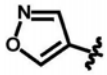
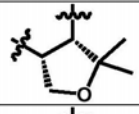
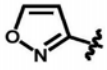
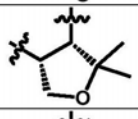
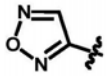
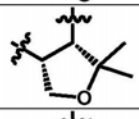
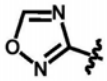
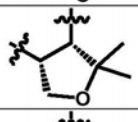
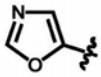
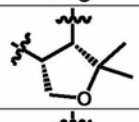
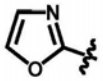
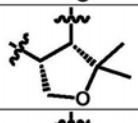
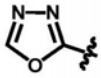
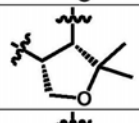
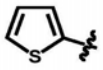
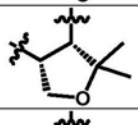
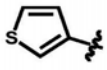
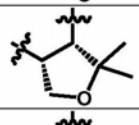
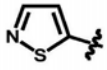
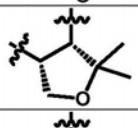
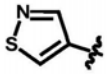
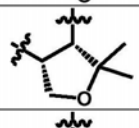
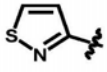
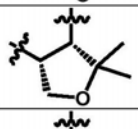
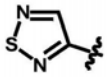
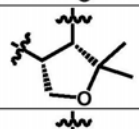
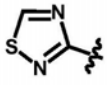
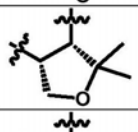
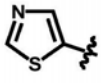
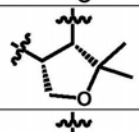
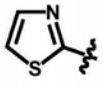
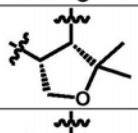
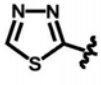
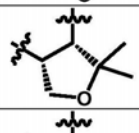
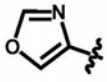
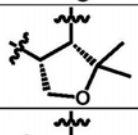
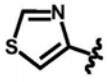
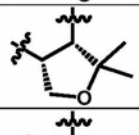
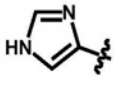
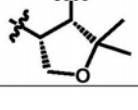
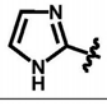
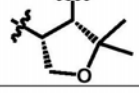
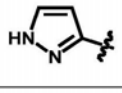
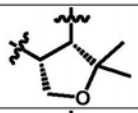
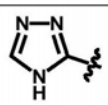
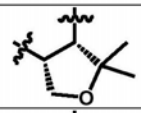
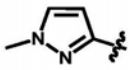
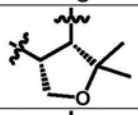
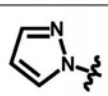
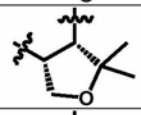
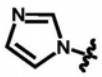
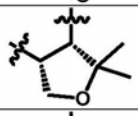
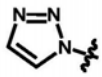
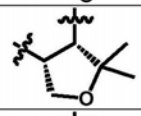
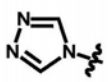
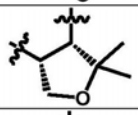
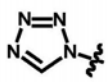
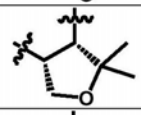
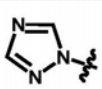
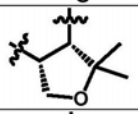
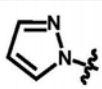
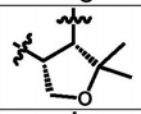
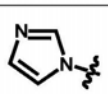
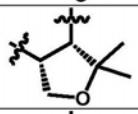
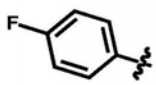
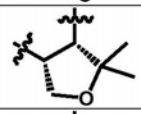
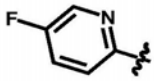
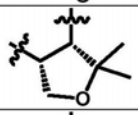
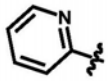
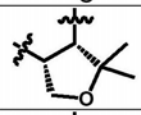
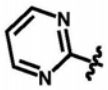
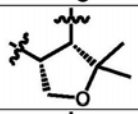
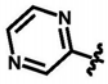
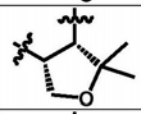
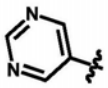
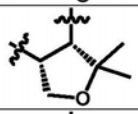
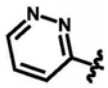
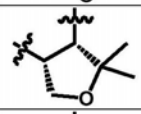
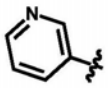
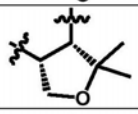
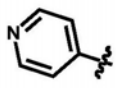
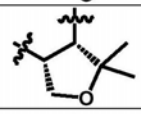
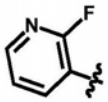
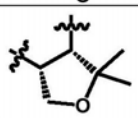
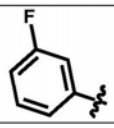
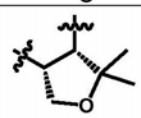
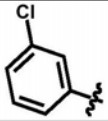
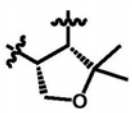
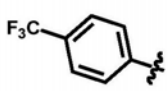
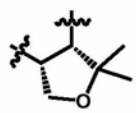
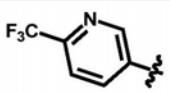
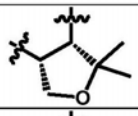
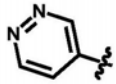
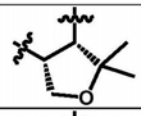
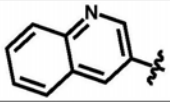
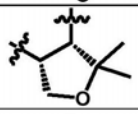
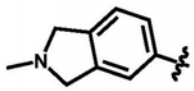
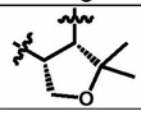
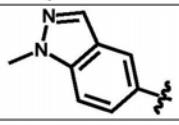
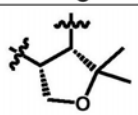
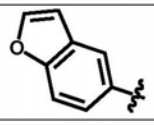
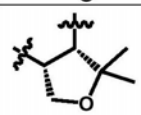
2-127			2-128		
2-129			2-130		
2-131			2-132		
2-133			2-134		
2-135			2-136		
2-137			2-138		
2-139			2-140		
2-141			2-142		
2-143			2-144		
2-145			2-146		
2-147			2-148		
2-149			2-150		
2-151			2-152		
2-153			2-154		
2-155			2-156		
2-157			2-158		

[0182]

2-159			2-160		
2-161			2-162		
2-163			2-164		
2-165			2-166		
2-167			2-168		
2-169			2-170		
2-171			2-172		
2-173			2-174		
2-175			2-176		
2-177			2-178		
2-179			2-180		
2-181			2-182		
2-183			2-184		
2-185			2-186		
2-187			2-188		

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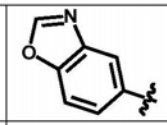
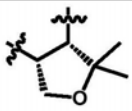
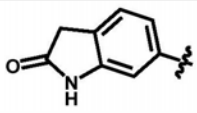
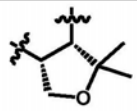
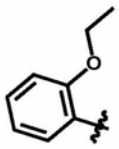
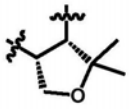
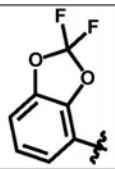
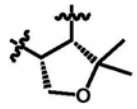
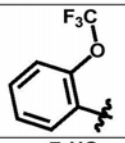
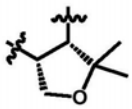
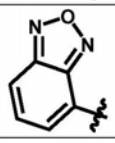
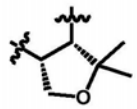
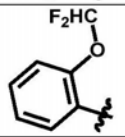
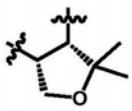
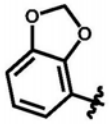
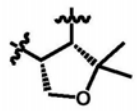
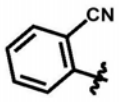
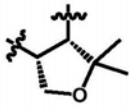
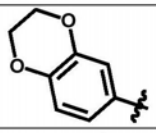
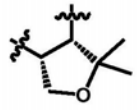
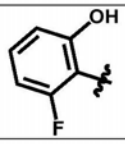
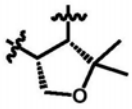
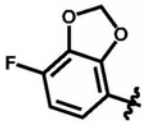
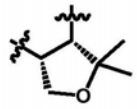
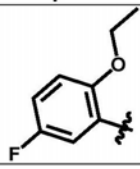
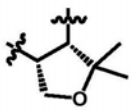
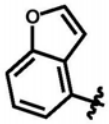
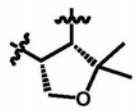
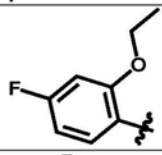
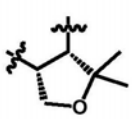
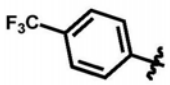
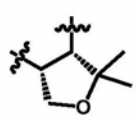
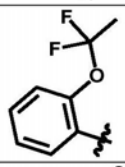
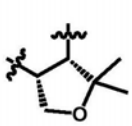
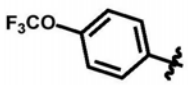
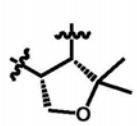
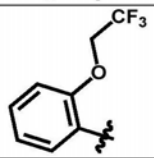
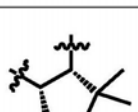
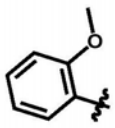
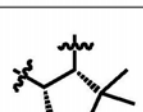
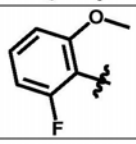
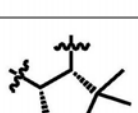
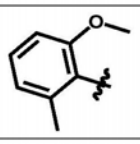
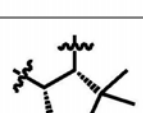
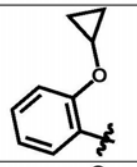
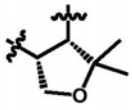
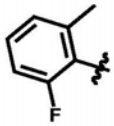
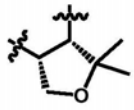
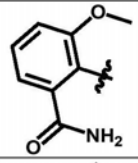
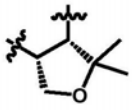
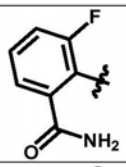
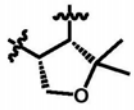
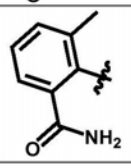
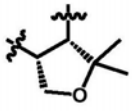
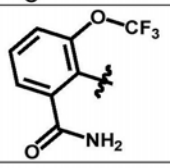
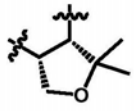
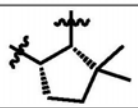
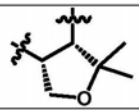
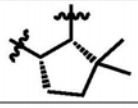
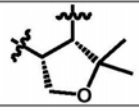
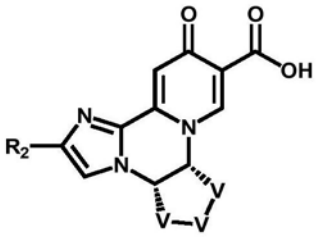
2-189			2-190		
2-191			2-192		
2-193			2-194		
2-195			2-196		
2-197			2-198		
2-199			2-200		
2-201			2-202		
2-203			2-204		
2-205			2-206		
2-207			2-208		
2-209			2-210		

[0184]

2-211			2-212		
2-213			2-214		
2-215			2-216		
2-217			2-218		
2-219			2-220		

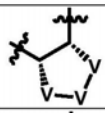
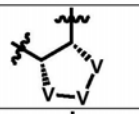
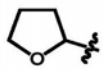
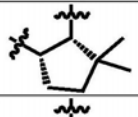
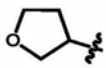
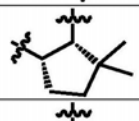
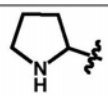
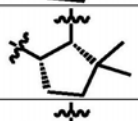
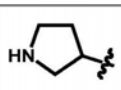
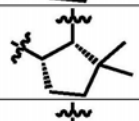
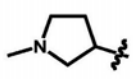
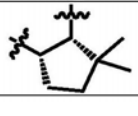
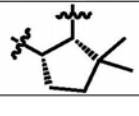
[0185] 本发明的代表性化合物包括但不限于根据式(X-3)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2和 在表3中定义。

[0186] 

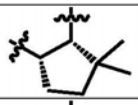
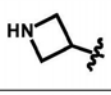
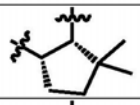
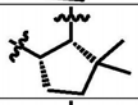
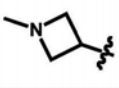
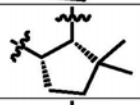
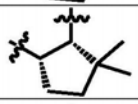
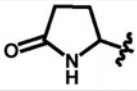
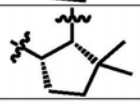
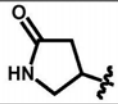
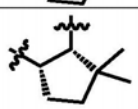
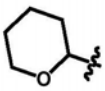
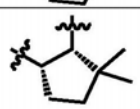
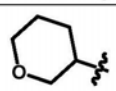
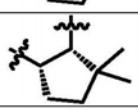
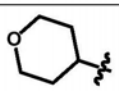
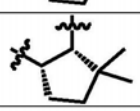
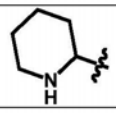
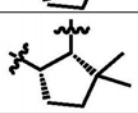
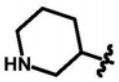
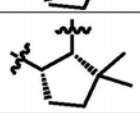
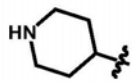
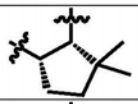
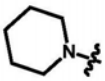
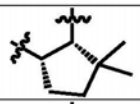
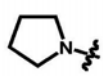
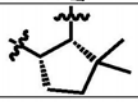
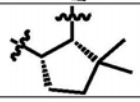
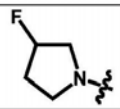
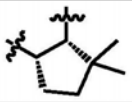
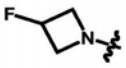
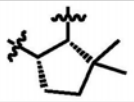
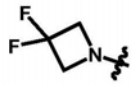
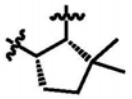
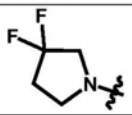
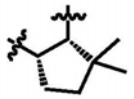
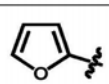
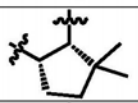
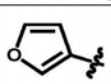
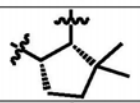
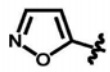
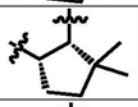
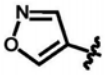
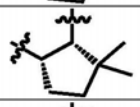
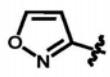
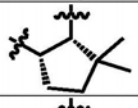
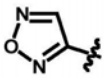
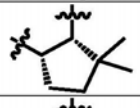
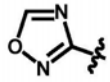
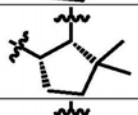
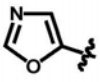
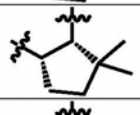
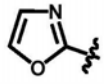
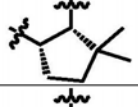
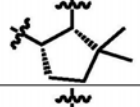
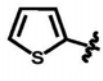
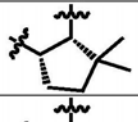
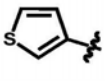
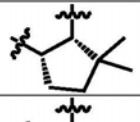
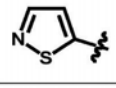
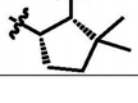
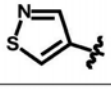
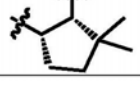
(X-3)

[0187] 表3

[0188]

化合物	R_2		化合物	R_2	
3-1			3-2		
3-3			3-4		
3-5			3-6		

[0189]

3-7			3-8		
3-9			3-10		
3-11			3-12		
3-13			3-14		
3-15			3-16		
3-17			3-18		
3-19			3-20		
3-21			3-22		
3-23			3-24		
3-25			3-26		
3-27			3-28		
3-29			3-30		
3-31			3-32		
3-33			3-34		
3-35			3-36		
3-37			3-38		
3-39			3-40		

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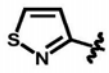
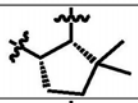
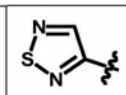
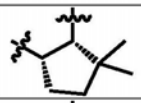
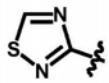
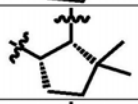
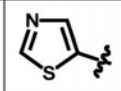
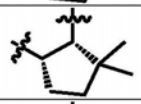
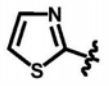
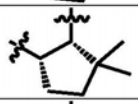
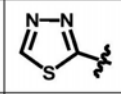
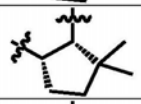
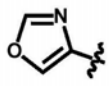
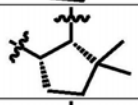
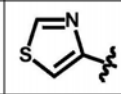
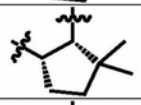
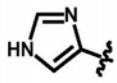
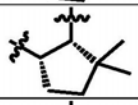
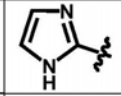
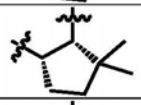
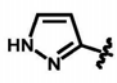
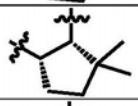
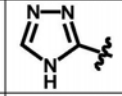
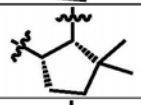
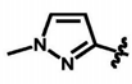
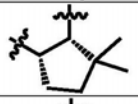
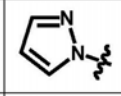
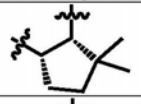
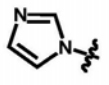
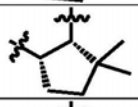
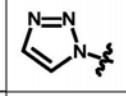
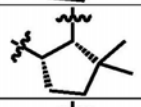
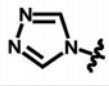
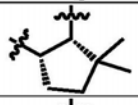
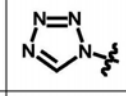
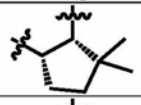
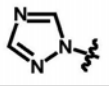
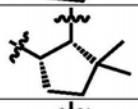
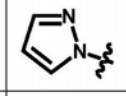
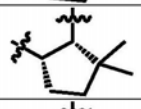
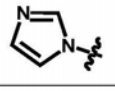
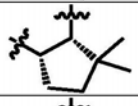
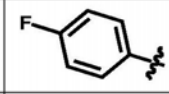
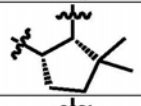
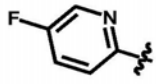
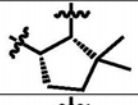
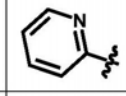
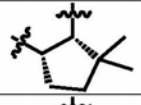
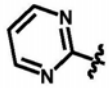
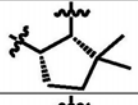
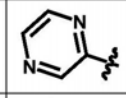
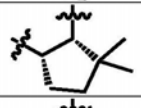
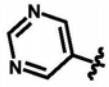
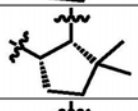
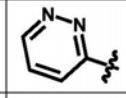
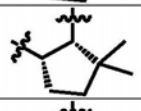
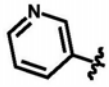
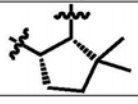
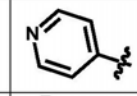
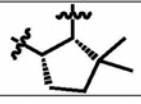
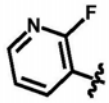
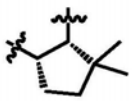
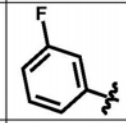
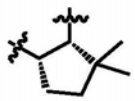
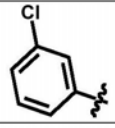
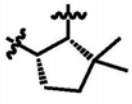
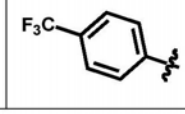
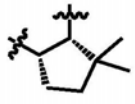
3-41			3-42		
3-43			3-44		
3-45			3-46		
3-47			3-48		
3-49			3-50		
3-51			3-52		
3-53			3-54		
3-55			3-56		
3-57			3-58		
3-59			3-60		
3-61			3-62		
3-63			3-64		
3-65			3-66		
3-67			3-68		
3-69			3-70		
3-71			3-72		
3-73			3-74		

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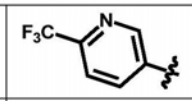
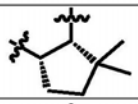
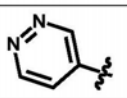
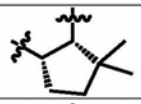
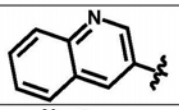
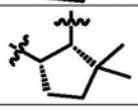
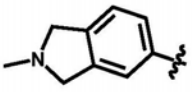
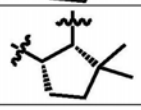
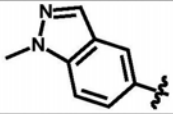
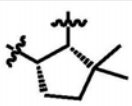
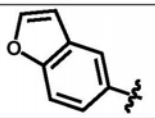
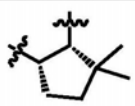
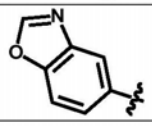
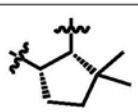
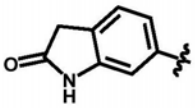
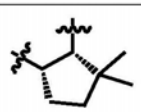
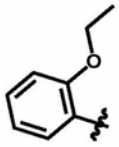
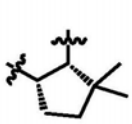
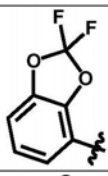
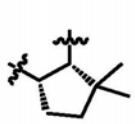
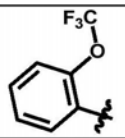
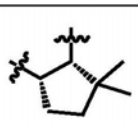
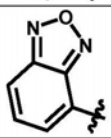
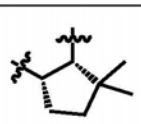
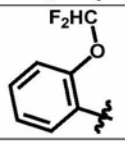
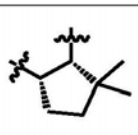
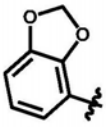
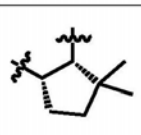
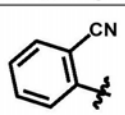
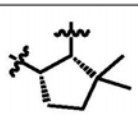
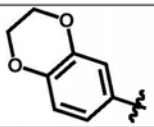
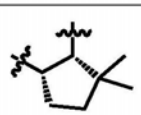
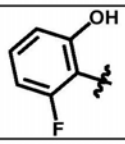
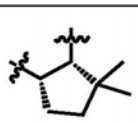
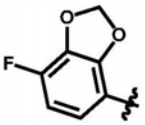
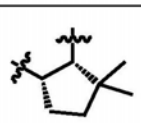
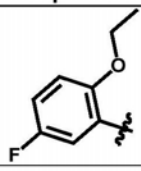
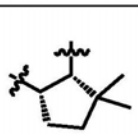
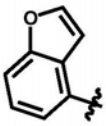
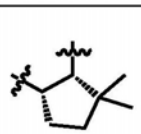
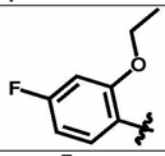
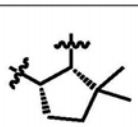
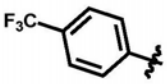
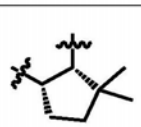
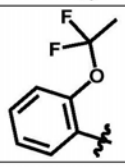
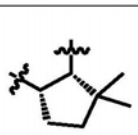
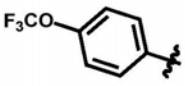
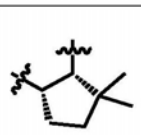
3-75			3-76		
3-77			3-78		
3-79			3-80		
3-81			3-82		
3-83			3-84		
3-85			3-86		
3-87			3-88		
3-89			3-90		
3-91			3-92		
3-93			3-94		
3-95			3-96		
3-97			3-98		

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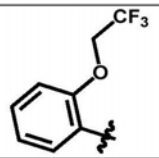
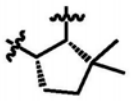
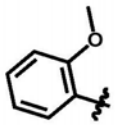
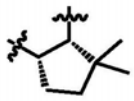
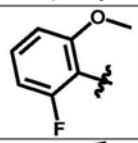
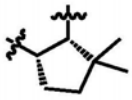
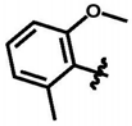
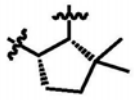
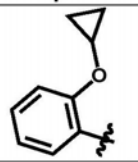
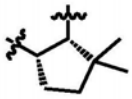
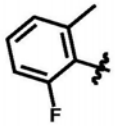
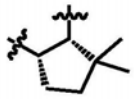
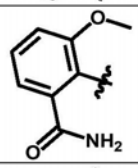
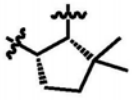
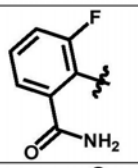
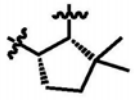
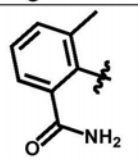
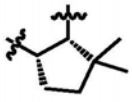
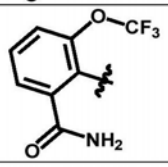
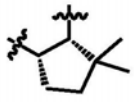
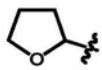
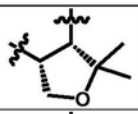
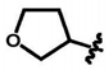
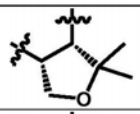
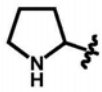
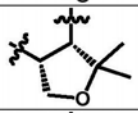
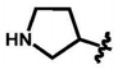
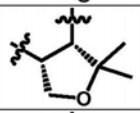
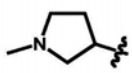
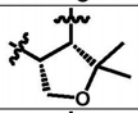
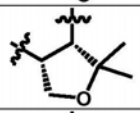
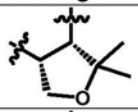
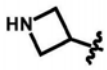
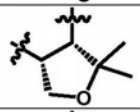
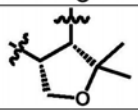
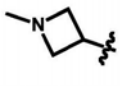
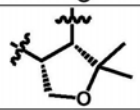
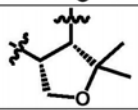
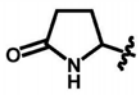
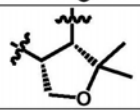
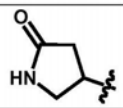
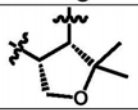
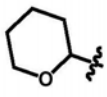
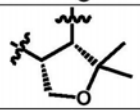
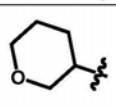
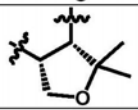
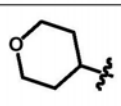
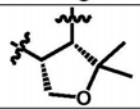
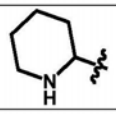
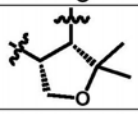
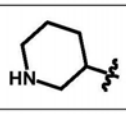
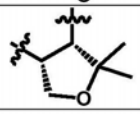
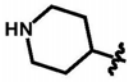
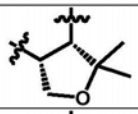
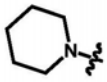
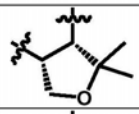
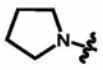
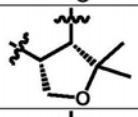
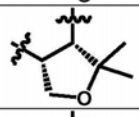
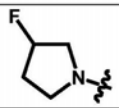
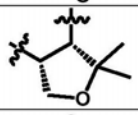
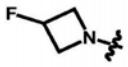
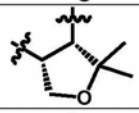
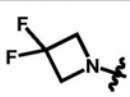
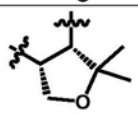
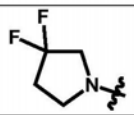
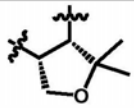
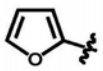
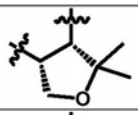
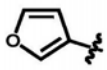
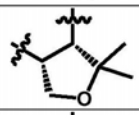
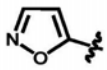
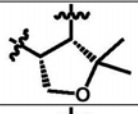
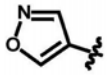
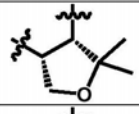
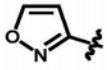
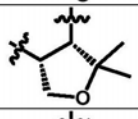
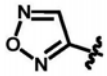
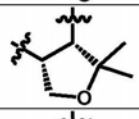
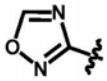
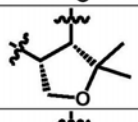
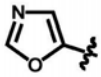
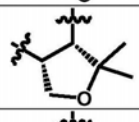
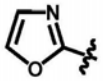
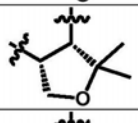
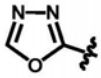
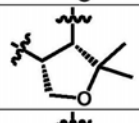
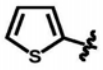
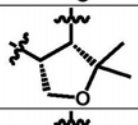
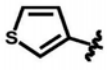
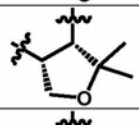
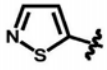
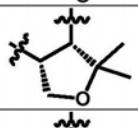
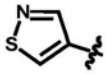
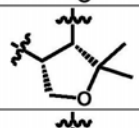
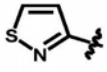
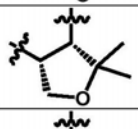
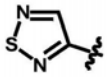
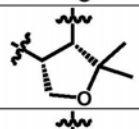
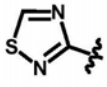
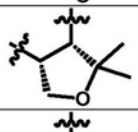
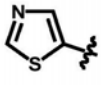
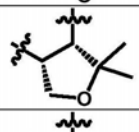
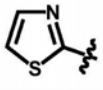
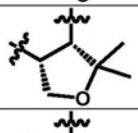
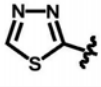
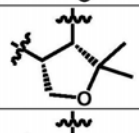
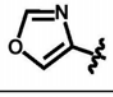
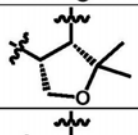
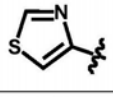
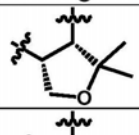
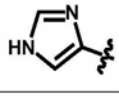
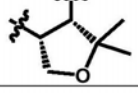
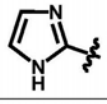
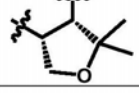
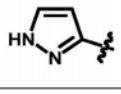
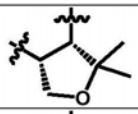
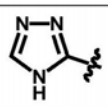
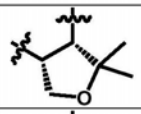
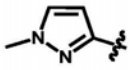
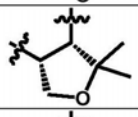
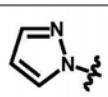
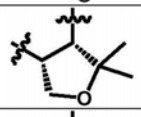
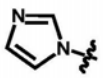
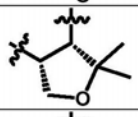
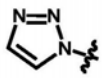
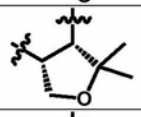
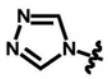
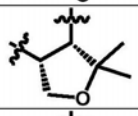
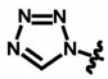
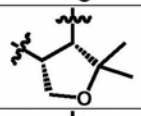
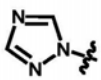
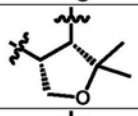
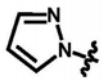
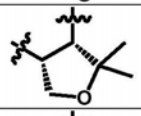
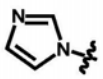
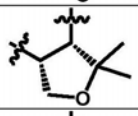
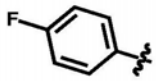
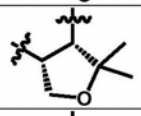
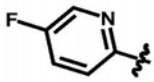
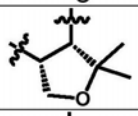
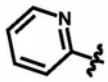
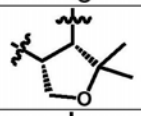
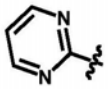
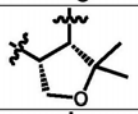
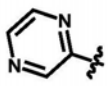
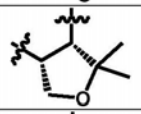
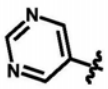
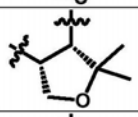
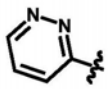
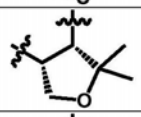
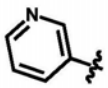
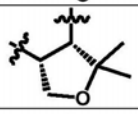
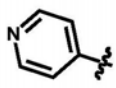
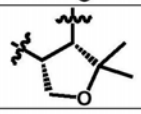
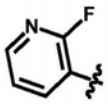
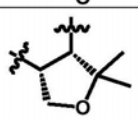
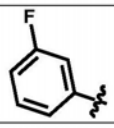
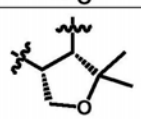
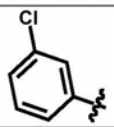
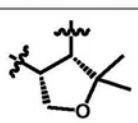
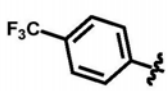
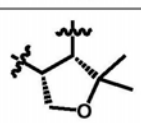
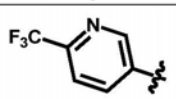
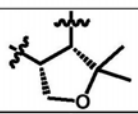
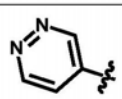
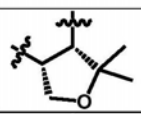
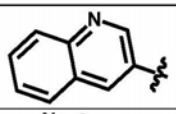
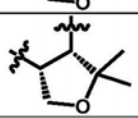
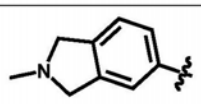
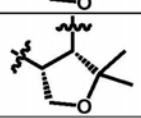
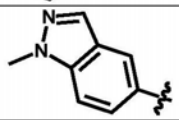
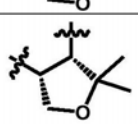
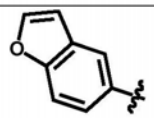
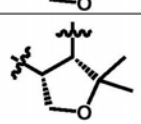
3-99			3-100		
3-101			3-102		
3-103			3-104		
3-105			3-106		
3-107			3-108		
3-109			3-110		
3-111			3-112		
3-113			3-114		
3-115			3-116		
3-117			3-118		
3-119			3-120		
3-121			3-122		
3-123			3-124		
3-125			3-126		

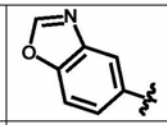
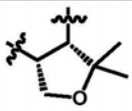
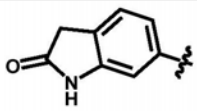
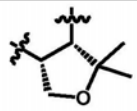
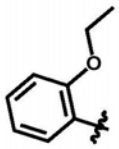
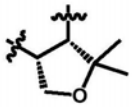
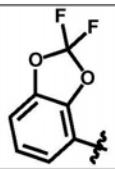
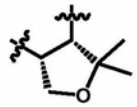
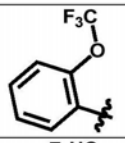
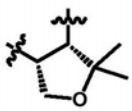
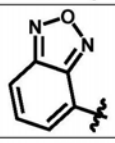
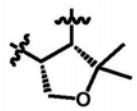
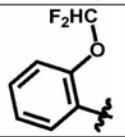
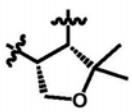
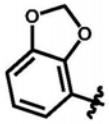
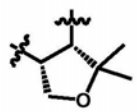
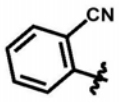
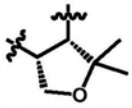
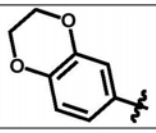
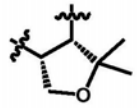
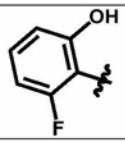
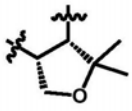
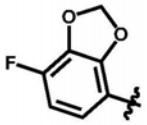
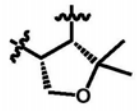
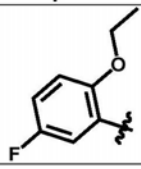
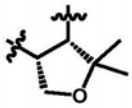
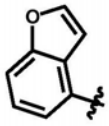
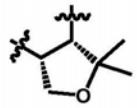
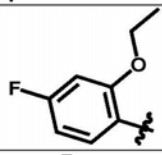
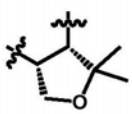
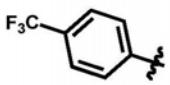
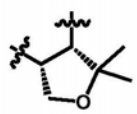
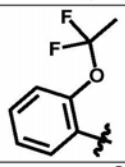
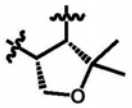
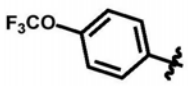
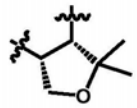
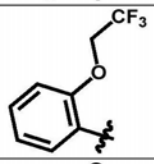
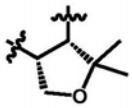
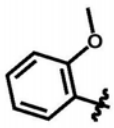
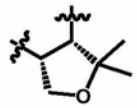
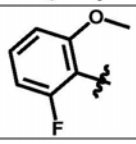
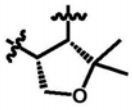
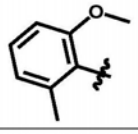
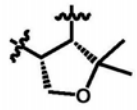
[0193]

3-127			3-128		
3-129			3-130		
3-131			3-132		
3-133			3-134		
3-135			3-136		
3-137			3-138		
3-139			3-140		
3-141			3-142		
3-143			3-144		
3-145			3-146		
3-147			3-148		
3-149			3-150		
3-151			3-152		
3-153			3-154		
3-155			3-156		
3-157			3-158		

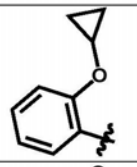
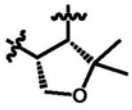
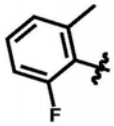
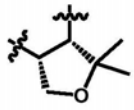
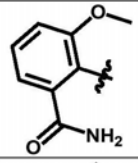
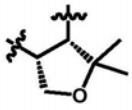
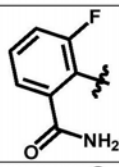
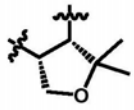
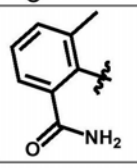
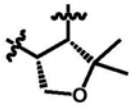
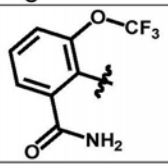
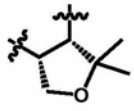
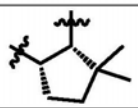
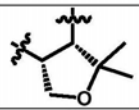
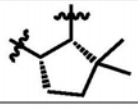
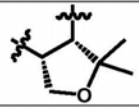
[0194]

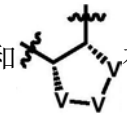
3-159			3-160		
3-161			3-162		
3-163			3-164		
3-165			3-166		
3-167			3-168		
3-169			3-170		
3-171			3-172		
3-173			3-174		
3-175			3-176		
3-177			3-178		
3-179			3-180		
3-181			3-182		
3-183			3-184		
3-185			3-186		
3-187			3-188		

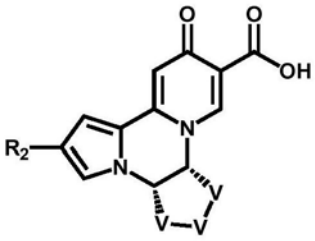
[0195]

3-189			3-190		
3-191			3-192		
3-193			3-194		
3-195			3-196		
3-197			3-198		
3-199			3-200		
3-201			3-202		
3-203			3-204		
3-205			3-206		
3-207			3-208		
3-209			3-210		

[0196]

3-211			3-212		
3-213			3-214		
3-215			3-216		
3-217			3-218		
3-219			3-220		

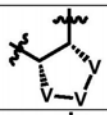
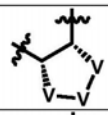
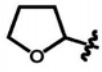
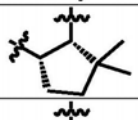
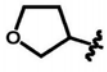
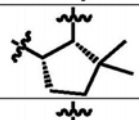
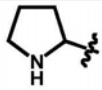
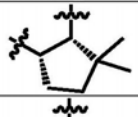
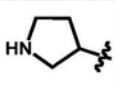
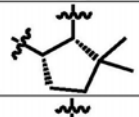
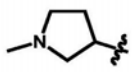
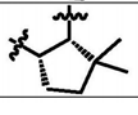
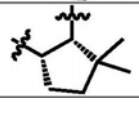
[0197] 本发明的代表性化合物包括但不限于根据式(X-4)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2和  在表4中定义。

[0198] 

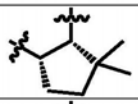
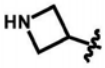
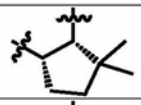
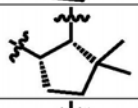
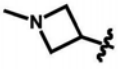
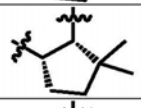
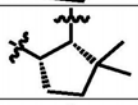
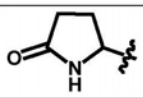
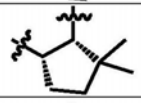
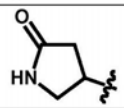
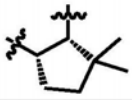
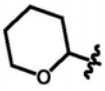
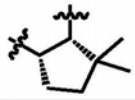
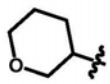
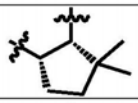
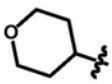
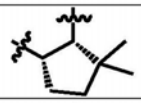
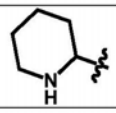
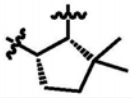
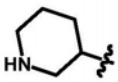
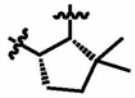
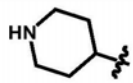
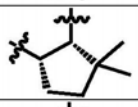
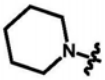
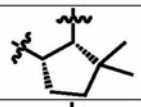
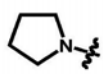
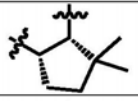
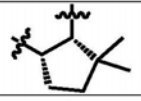
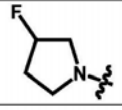
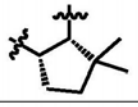
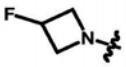
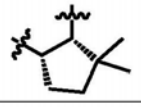
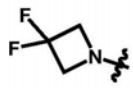
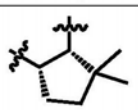
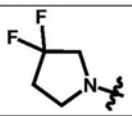
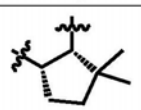
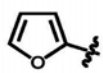
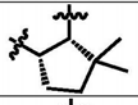
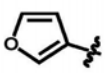
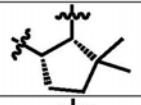
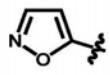
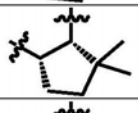
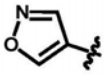
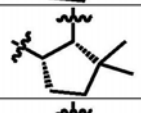
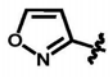
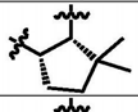
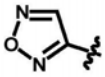
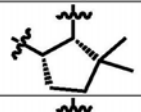
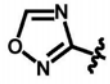
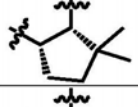
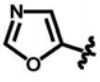
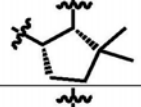
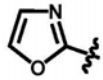
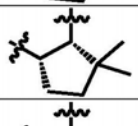
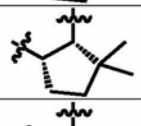
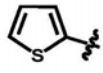
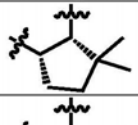
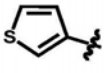
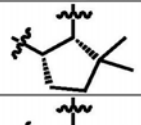
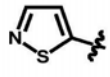
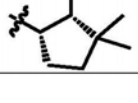
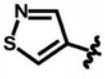
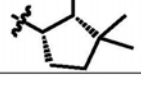
(X-4)

[0199] 表4

[0200]

化合物	R_2		化合物	R_2	
4-1			4-2		
4-3			4-4		
4-5			4-6		

[0201]

4-7			4-8		
4-9			4-10		
4-11			4-12		
4-13			4-14		
4-15			4-16		
4-17			4-18		
4-19			4-20		
4-21			4-22		
4-23			4-24		
4-25			4-26		
4-27			4-28		
4-29			4-30		
4-31			4-32		
4-33			4-34		
4-35			4-36		
4-37			4-38		
4-39			4-40		

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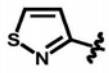
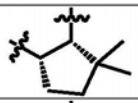
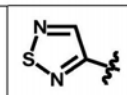
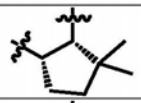
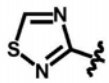
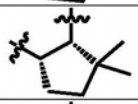
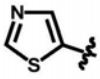
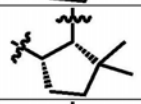
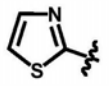
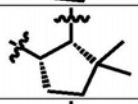
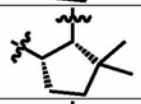
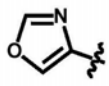
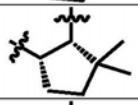
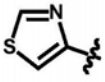
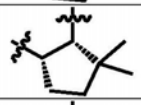
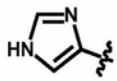
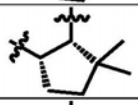
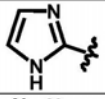
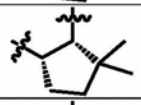
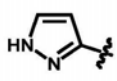
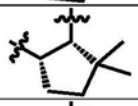
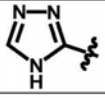
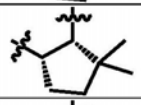
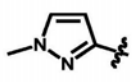
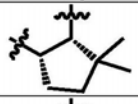
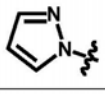
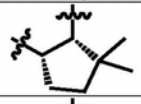
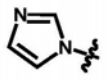
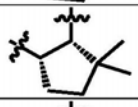
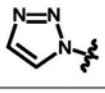
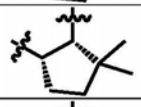
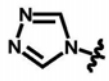
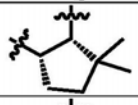
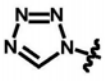
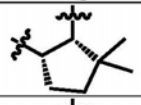
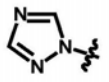
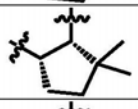
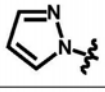
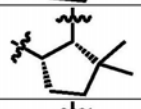
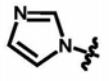
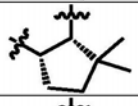
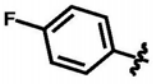
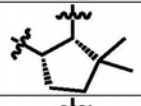
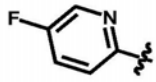
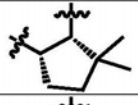
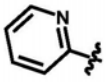
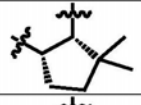
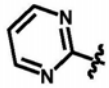
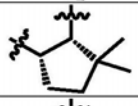
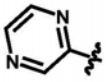
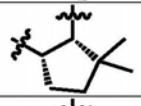
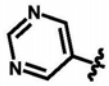
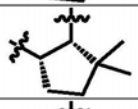
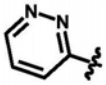
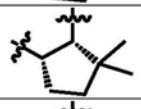
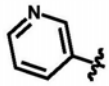
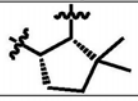
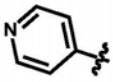
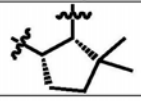
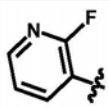
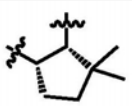
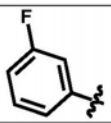
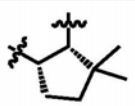
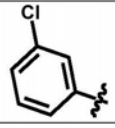
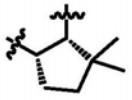
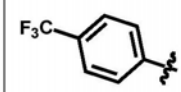
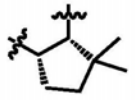
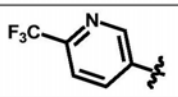
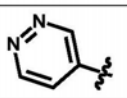
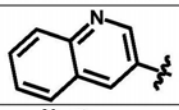
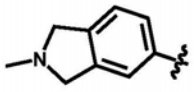
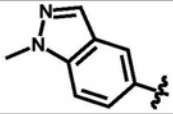
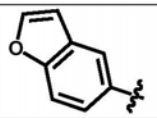
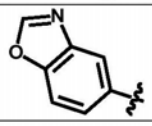
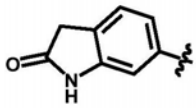
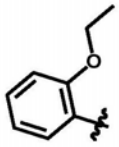
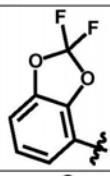
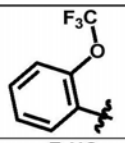
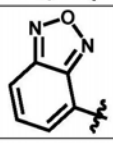
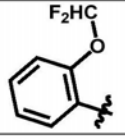
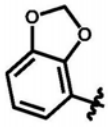
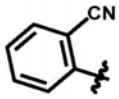
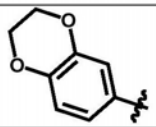
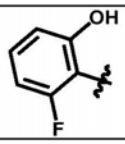
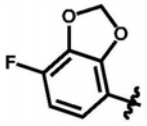
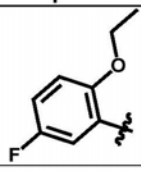
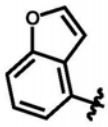
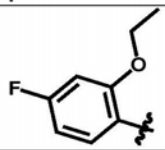
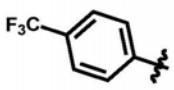
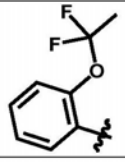
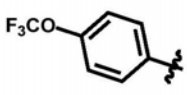
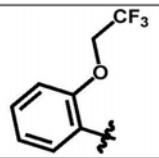
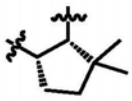
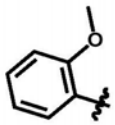
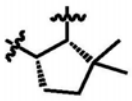
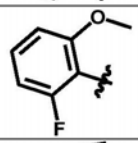
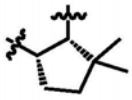
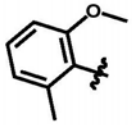
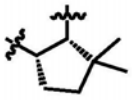
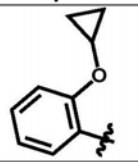
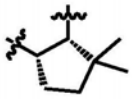
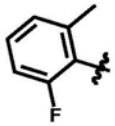
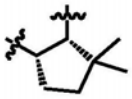
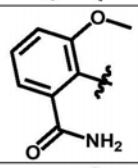
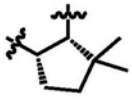
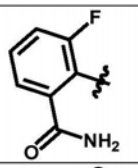
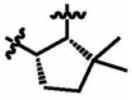
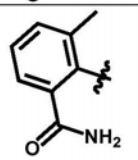
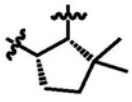
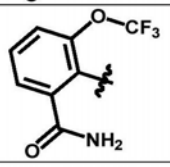
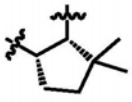
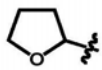
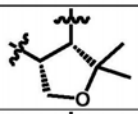
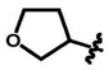
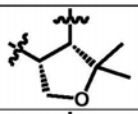
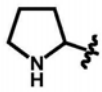
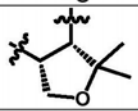
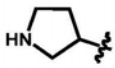
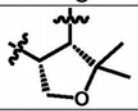
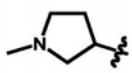
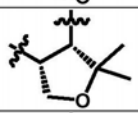
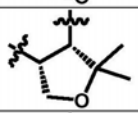
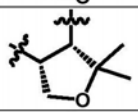
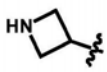
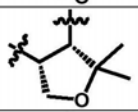
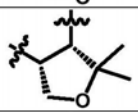
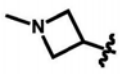
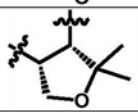
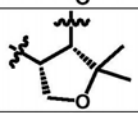
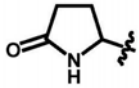
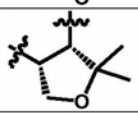
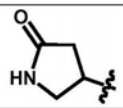
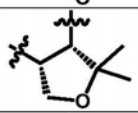
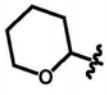
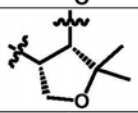
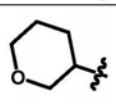
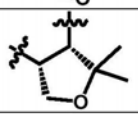
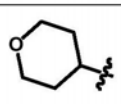
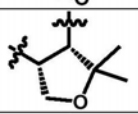
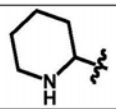
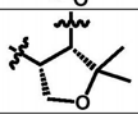
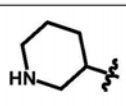
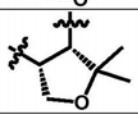
4-41			4-42		
4-43			4-44		
4-45			4-46		
4-47			4-48		
4-49			4-50		
4-51			4-52		
4-53			4-54		
4-55			4-56		
4-57			4-58		
4-59			4-60		
4-61			4-62		
4-63			4-64		
4-65			4-66		
4-67			4-68		
4-69			4-70		
4-71			4-72		
4-73			4-74		

[0203]

4-75			4-76		
4-77			4-78		
4-79			4-80		
4-81			4-82		
4-83			4-84		
4-85			4-86		
4-87			4-88		
4-89			4-90		
4-91			4-92		
4-93			4-94		
4-95			4-96		
4-97			4-98		

[0204]

4-99			4-100		
4-101			4-102		
4-103			4-104		
4-105			4-106		
4-107			4-108		
4-109			4-110		
4-111			4-112		
4-113			4-114		
4-115			4-116		
4-117			4-118		
4-119			4-120		
4-121			4-122		
4-123			4-124		
4-125			4-126		

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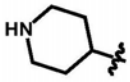
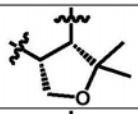
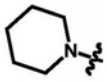
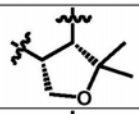
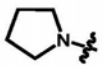
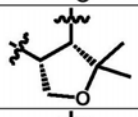
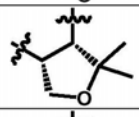
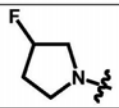
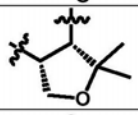
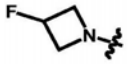
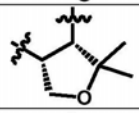
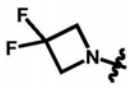
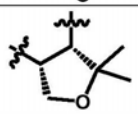
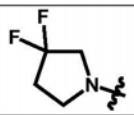
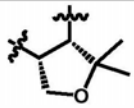
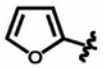
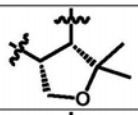
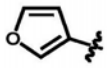
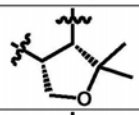
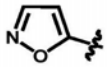
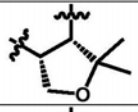
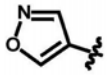
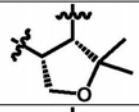
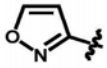
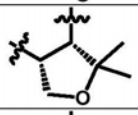
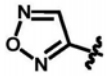
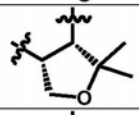
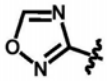
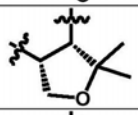
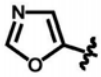
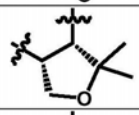
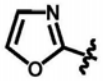
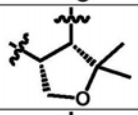
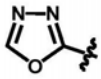
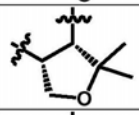
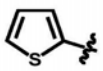
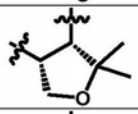
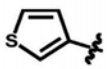
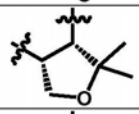
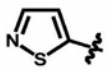
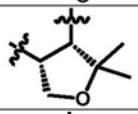
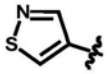
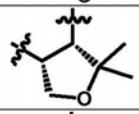
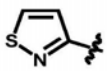
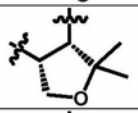
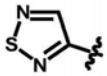
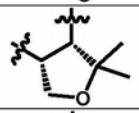
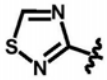
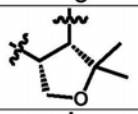
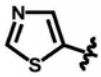
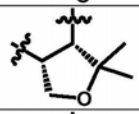
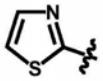
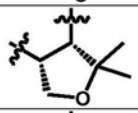
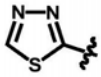
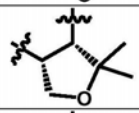
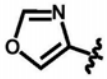
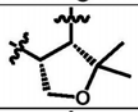
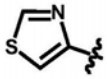
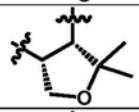
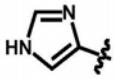
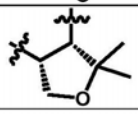
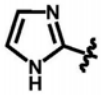
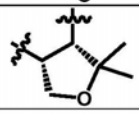
4-127			4-128		
4-129			4-130		
4-131			4-132		
4-133			4-134		
4-135			4-136		
4-137			4-138		
4-139			4-140		
4-141			4-142		
4-143			4-144		
4-145			4-146		
4-147			4-148		
4-149			4-150		
4-151			4-152		
4-153			4-154		
4-155			4-156		
4-157			4-158		

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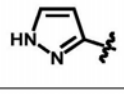
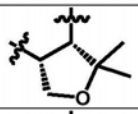
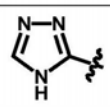
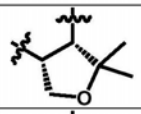
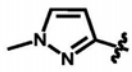
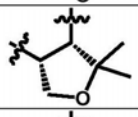
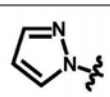
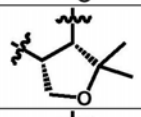
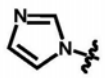
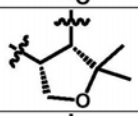
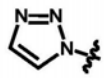
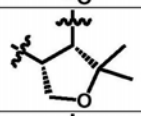
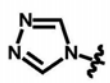
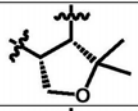
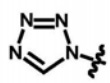
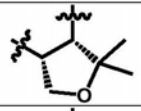
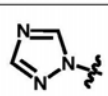
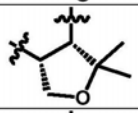
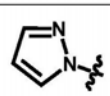
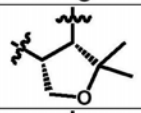
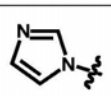
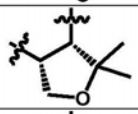
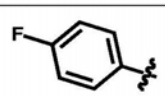
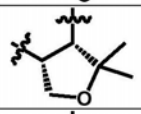
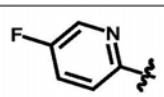
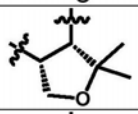
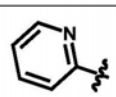
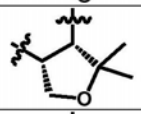
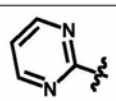
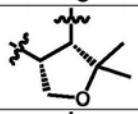
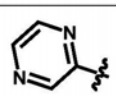
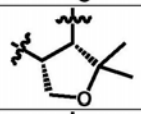
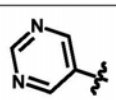
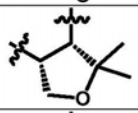
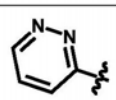
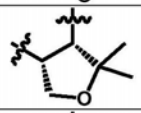
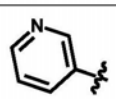
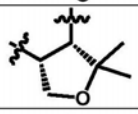
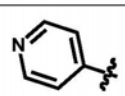
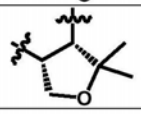
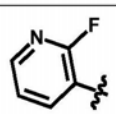
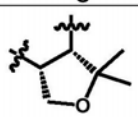
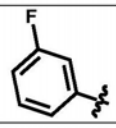
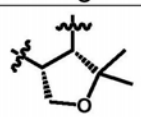
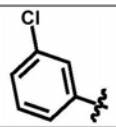
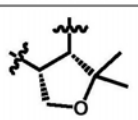
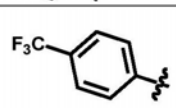
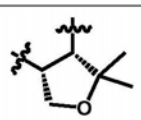
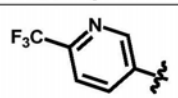
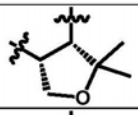
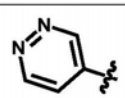
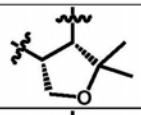
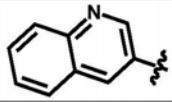
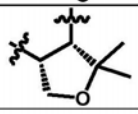
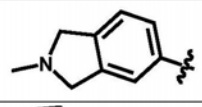
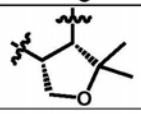
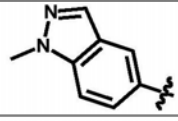
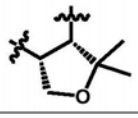
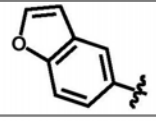
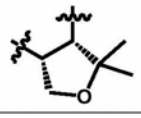
4-159			4-160		
4-161			4-162		
4-163			4-164		
4-165			4-166		
4-167			4-168		
4-169			4-170		
4-171			4-172		
4-173			4-174		
4-175			4-176		
4-177			4-178		
4-179			4-180		
4-181			4-182		
4-183			4-184		
4-185			4-186		
4-187			4-188		

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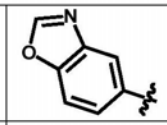
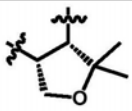
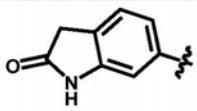
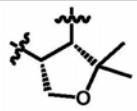
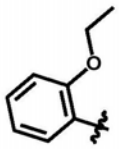
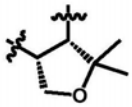
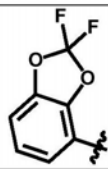
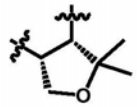
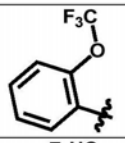
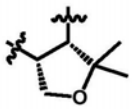
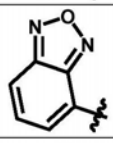
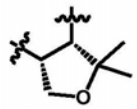
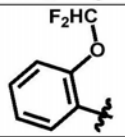
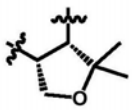
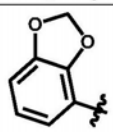
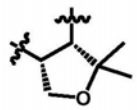
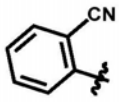
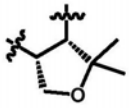
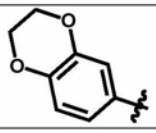
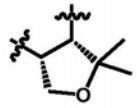
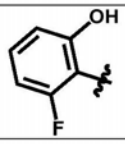
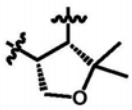
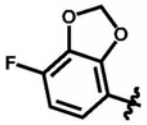
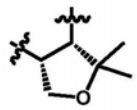
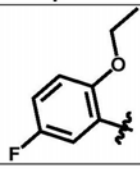
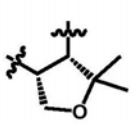
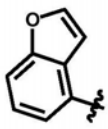
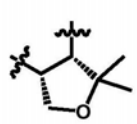
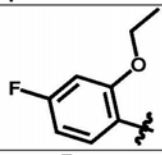
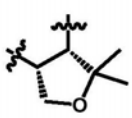
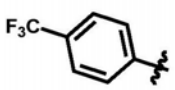
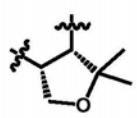
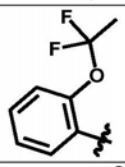
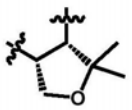
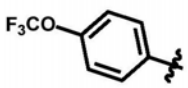
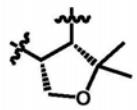
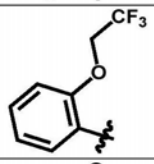
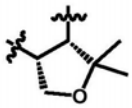
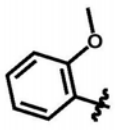
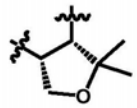
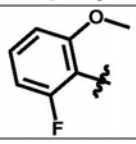
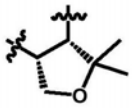
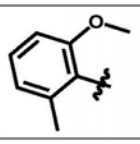
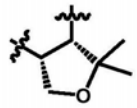
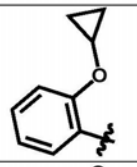
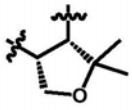
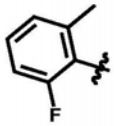
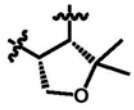
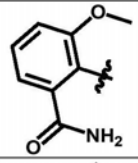
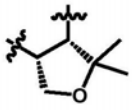
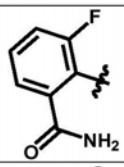
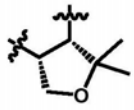
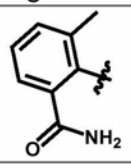
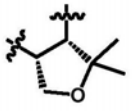
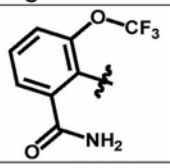
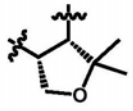
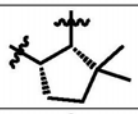
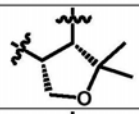
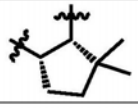
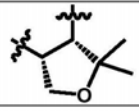
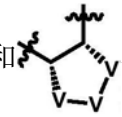
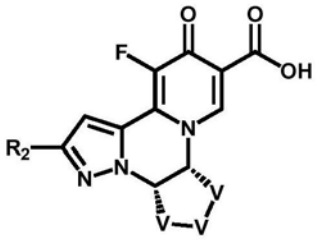
4-189			4-190		
4-191			4-192		
4-193			4-194		
4-195			4-196		
4-197			4-198		
4-199			4-200		
4-201			4-202		
4-203			4-204		
4-205			4-206		
4-207			4-208		
4-209			4-210		

[0208]

4-211			4-212		
4-213			4-214		
4-215			4-216		
4-217			4-218		
4-219			4-220		

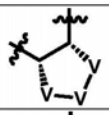
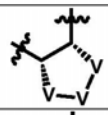
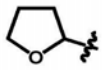
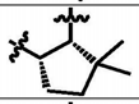
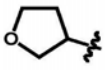
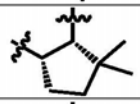
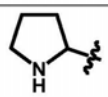
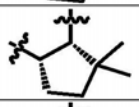
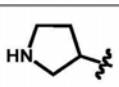
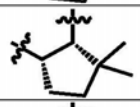
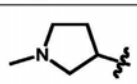
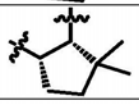
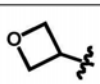
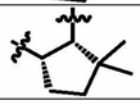
[0209] 本发明的代表性化合物包括但不限于根据式(X-5)的化合物，及其药学上可接受的盐，其中每一种化合物的R_2和  在表5中定义。

[0210] 

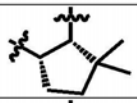
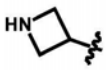
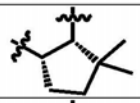
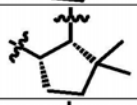
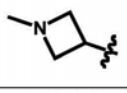
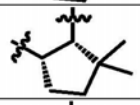
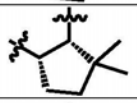
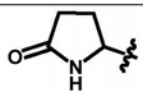
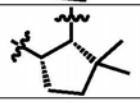
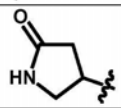
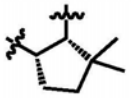
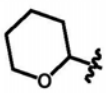
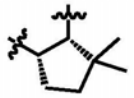
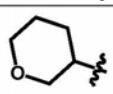
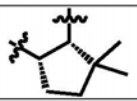
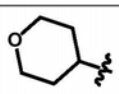
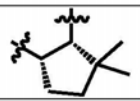
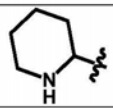
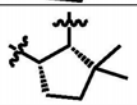
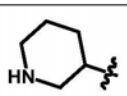
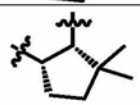
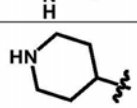
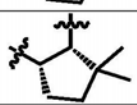
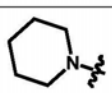
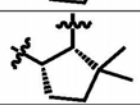
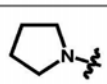
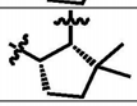
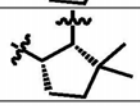
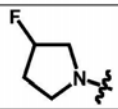
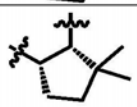
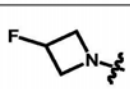
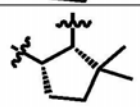
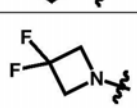
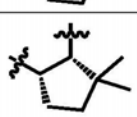
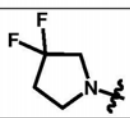
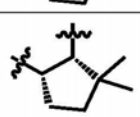
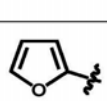
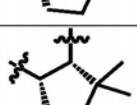
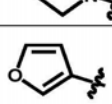
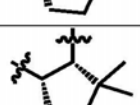
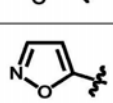
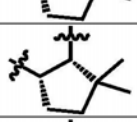
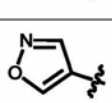
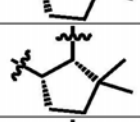
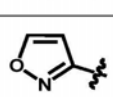
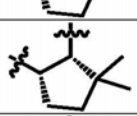
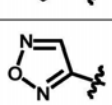
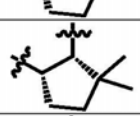
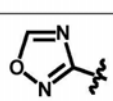
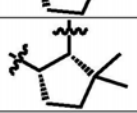
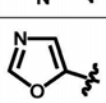
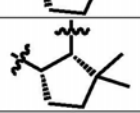
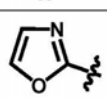
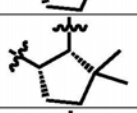
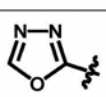
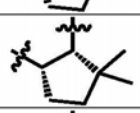
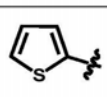
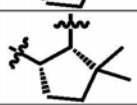
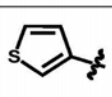
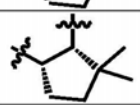
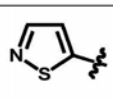
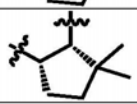
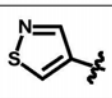
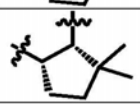
(X-5)

[0211] 表5

[0212]

化合物	R_2		化合物	R_2	
5-1			5-2		
5-3			5-4		
5-5			5-6		

[0213]

5-7			5-8		
5-9			5-10		
5-11			5-12		
5-13			5-14		
5-15			5-16		
5-17			5-18		
5-19			5-20		
5-21			5-22		
5-23			5-24		
5-25			5-26		
5-27			5-28		
5-29			5-30		
5-31			5-32		
5-33			5-34		
5-35			5-36		
5-37			5-38		
5-39			5-40		

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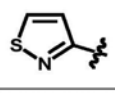
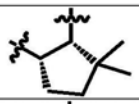
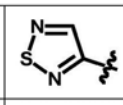
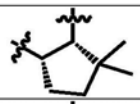
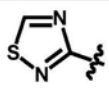
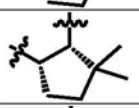
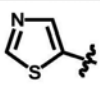
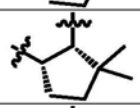
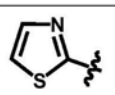
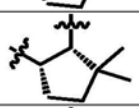
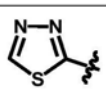
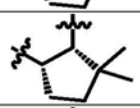
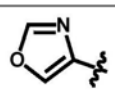
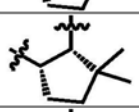
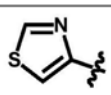
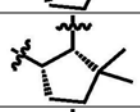
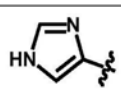
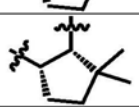
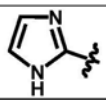
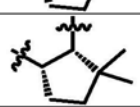
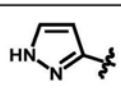
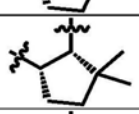
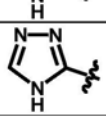
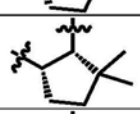
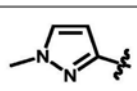
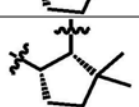
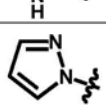
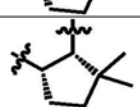
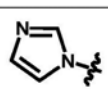
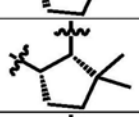
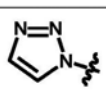
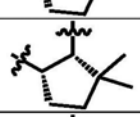
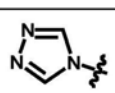
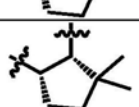
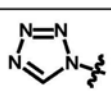
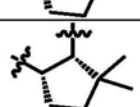
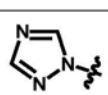
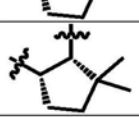
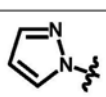
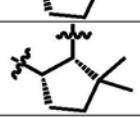
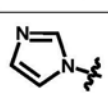
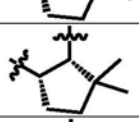
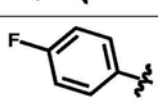
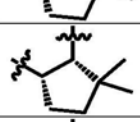
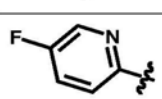
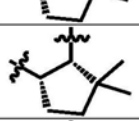
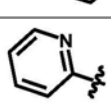
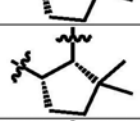
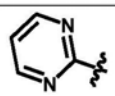
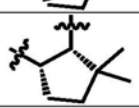
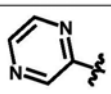
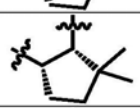
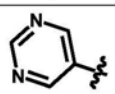
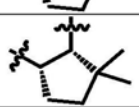
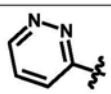
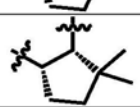
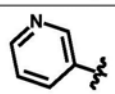
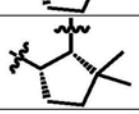
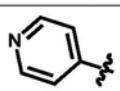
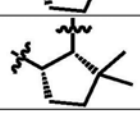
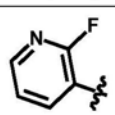
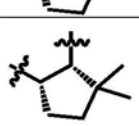
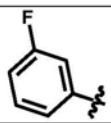
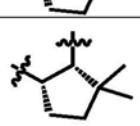
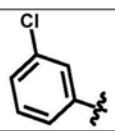
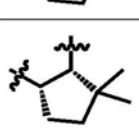
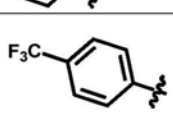
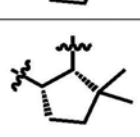
5-41			5-42		
5-43			5-44		
5-45			5-46		
5-47			5-48		
5-49			5-50		
5-51			5-52		
5-53			5-54		
5-55			5-56		
5-57			5-58		
5-59			5-60		
5-61			5-62		
5-63			5-64		
5-65			5-66		
5-67			5-68		
5-69			5-70		
5-71			5-72		
5-73			5-74		

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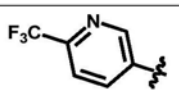
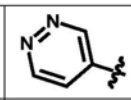
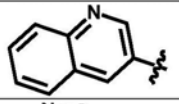
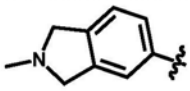
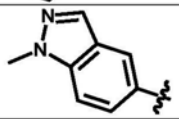
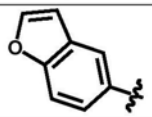
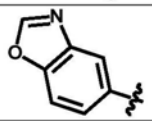
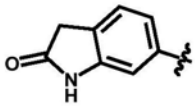
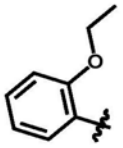
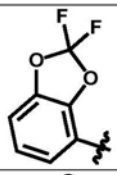
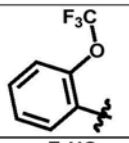
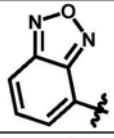
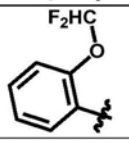
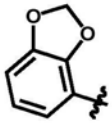
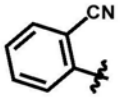
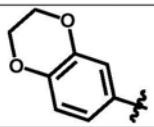
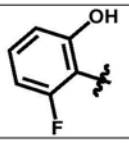
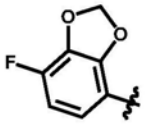
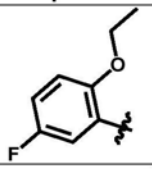
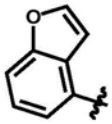
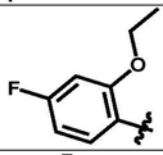
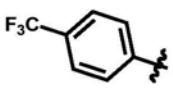
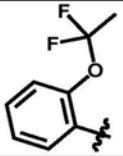
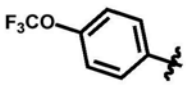
5-75			5-76		
5-77			5-78		
5-79			5-80		
5-81			5-82		
5-83			5-84		
5-85			5-86		
5-87			5-88		
5-89			5-90		
5-91			5-92		
5-93			5-94		
5-95			5-96		
5-97			5-98		

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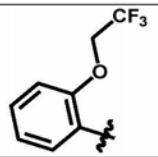
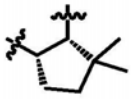
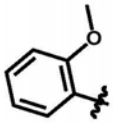
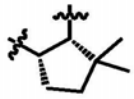
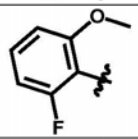
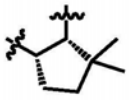
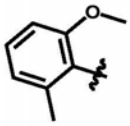
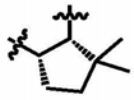
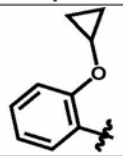
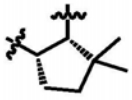
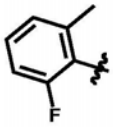
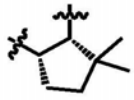
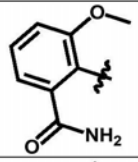
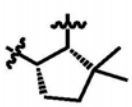
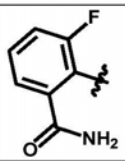
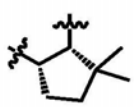
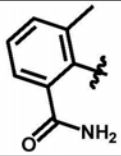
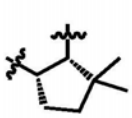
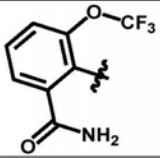
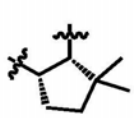
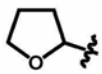
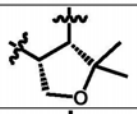
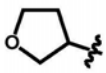
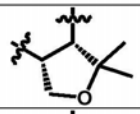
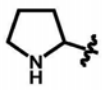
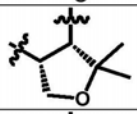
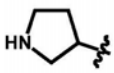
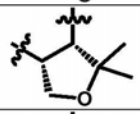
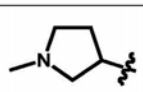
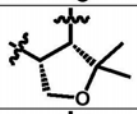
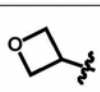
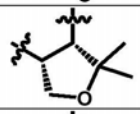
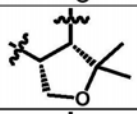
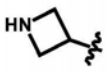
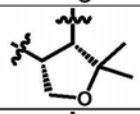
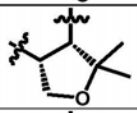
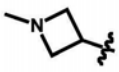
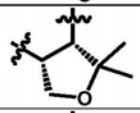
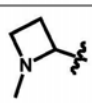
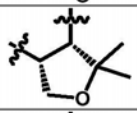
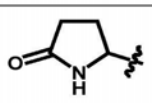
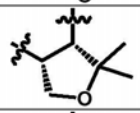
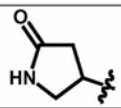
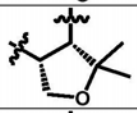
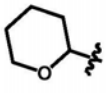
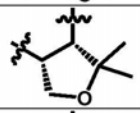
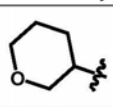
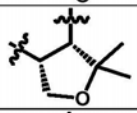
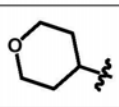
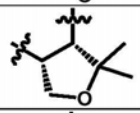
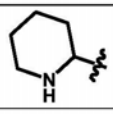
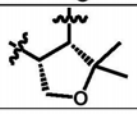
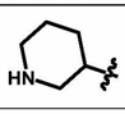
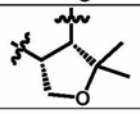
5-99			5-100		
5-101			5-102		
5-103			5-104		
5-105			5-106		
5-107			5-108		
5-109			5-110		
5-111			5-112		
5-113			5-114		
5-115			5-116		
5-117			5-118		
5-119			5-120		
5-121			5-122		
5-123			5-124		
5-125			5-126		

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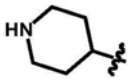
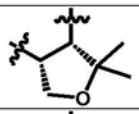
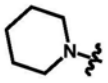
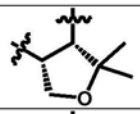
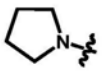
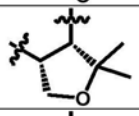
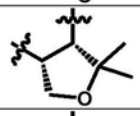
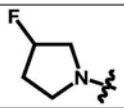
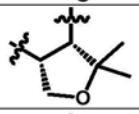
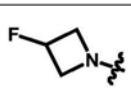
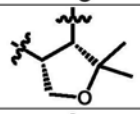
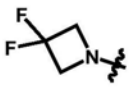
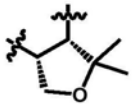
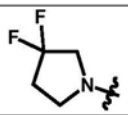
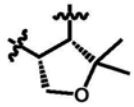
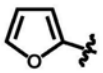
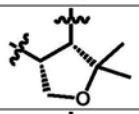
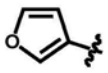
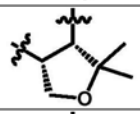
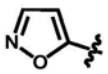
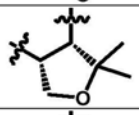
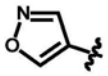
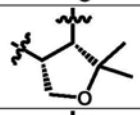
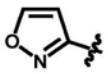
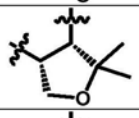
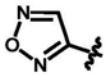
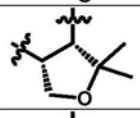
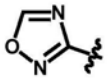
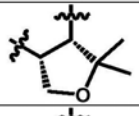
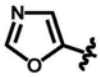
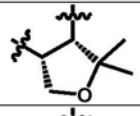
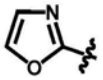
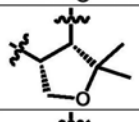
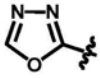
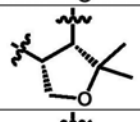
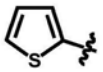
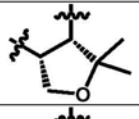
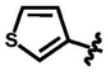
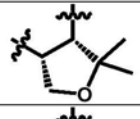
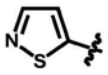
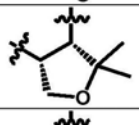
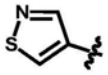
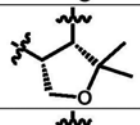
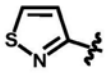
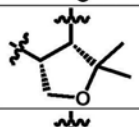
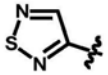
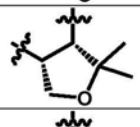
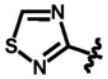
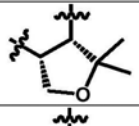
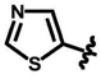
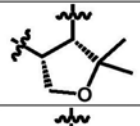
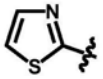
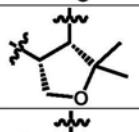
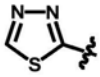
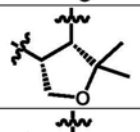
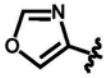
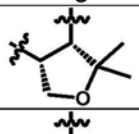
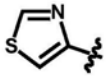
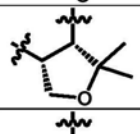
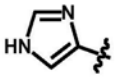
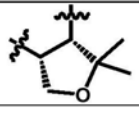
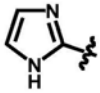
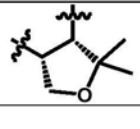
5-127			5-128		
5-129			5-130		
5-131			5-132		
5-133			5-134		
5-135			5-136		
5-137			5-138		
5-139			5-140		
5-141			5-142		
5-143			5-144		
5-145			5-146		
5-147			5-148		
5-149			5-150		
5-151			5-152		
5-153			5-154		
5-155			5-156		
5-157			5-158		

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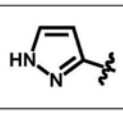
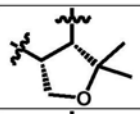
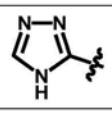
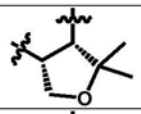
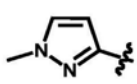
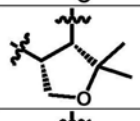
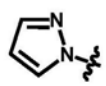
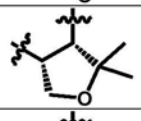
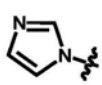
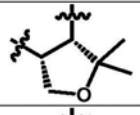
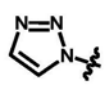
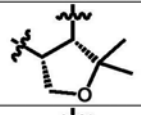
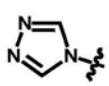
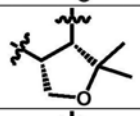
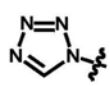
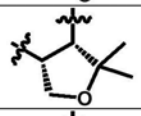
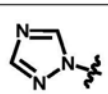
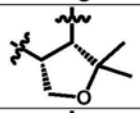
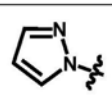
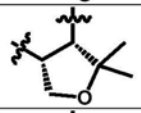
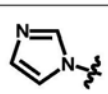
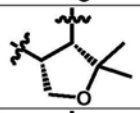
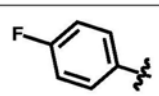
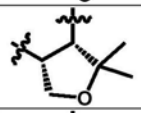
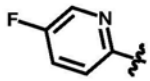
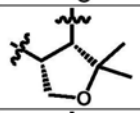
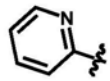
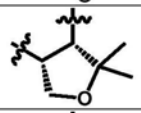
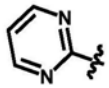
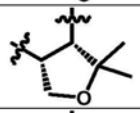
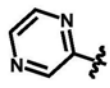
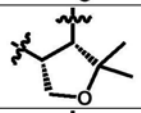
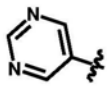
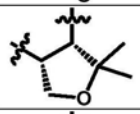
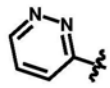
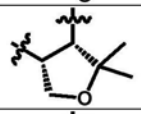
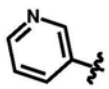
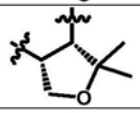
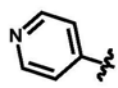
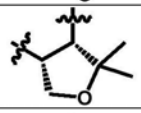
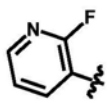
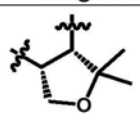
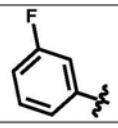
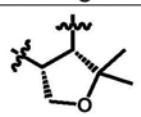
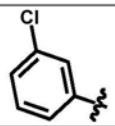
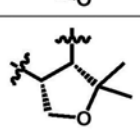
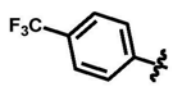
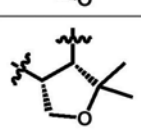
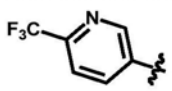
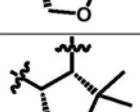
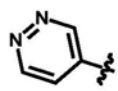
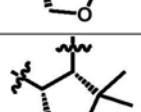
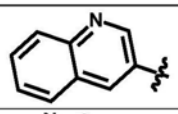
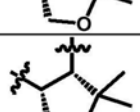
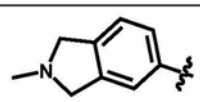
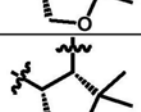
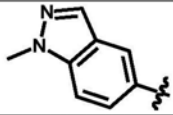
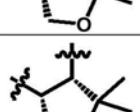
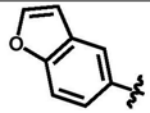
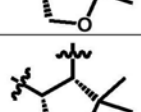
5-159			5-160		
5-161			5-162		
5-163			5-164		
5-165			5-166		
5-167			5-168		
5-169			5-170		
5-171			5-172		
5-173			5-174		
5-175			5-176		
5-177			5-178		
5-179			5-180		
5-181			5-182		
5-183			5-184		
5-185			5-186		
5-187			5-188		

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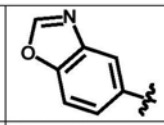
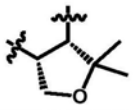
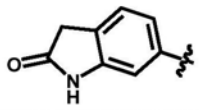
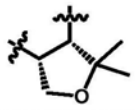
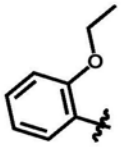
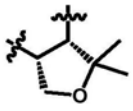
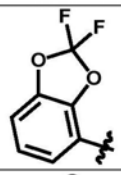
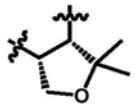
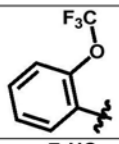
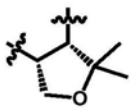
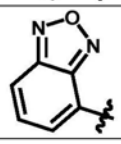
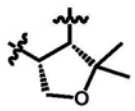
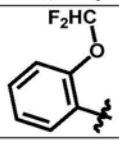
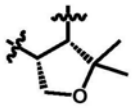
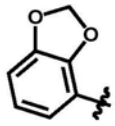
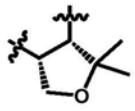
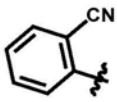
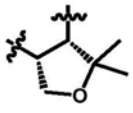
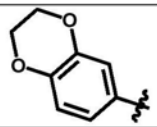
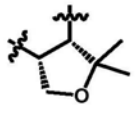
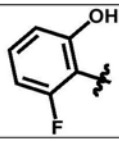
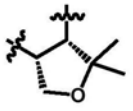
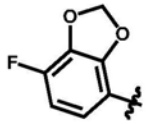
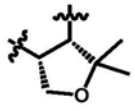
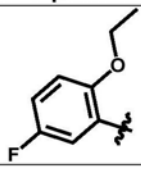
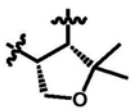
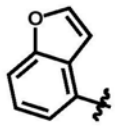
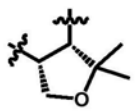
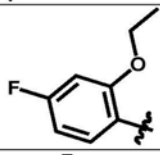
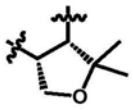
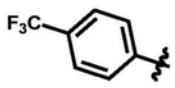
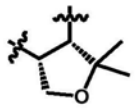
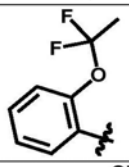
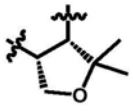
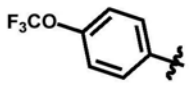
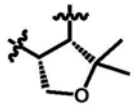
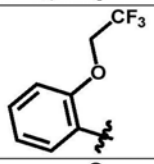
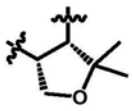
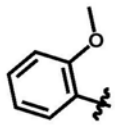
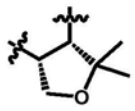
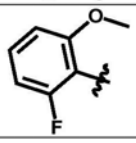
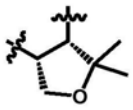
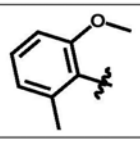
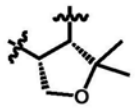
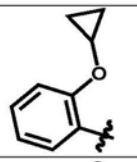
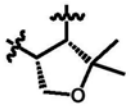
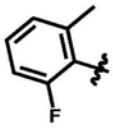
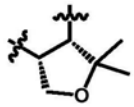
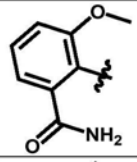
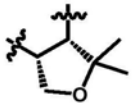
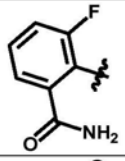
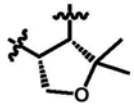
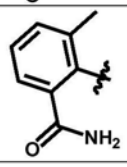
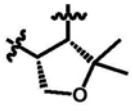
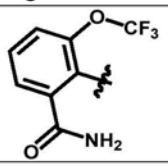
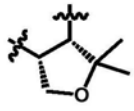
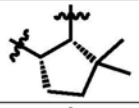
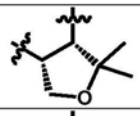
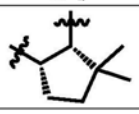
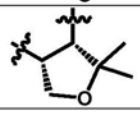
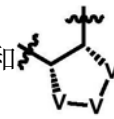
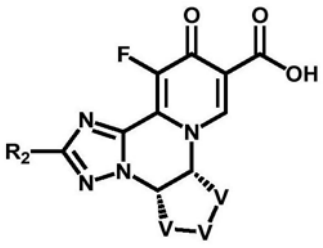
5-189			5-190		
5-191			5-192		
5-193			5-194		
5-195			5-196		
5-197			5-198		
5-199			5-200		
5-201			5-202		
5-203			5-204		
5-205			5-206		
5-207			5-208		
5-209			5-210		

[0220]

5-211			5-212		
5-213			5-214		
5-215			5-216		
5-217			5-218		
5-219			5-220		

[0221] 本发明的代表性化合物包括但不限于根据式(X-6)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2和  在表6中定义。

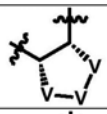
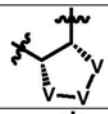
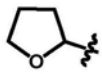
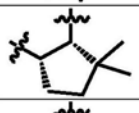
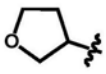
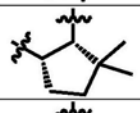
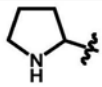
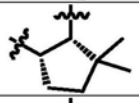
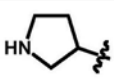
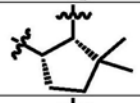
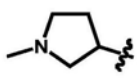
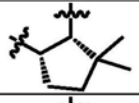
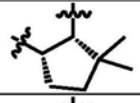
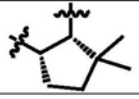
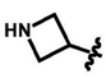
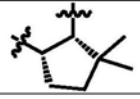
[0222]



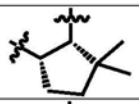
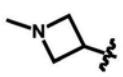
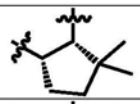
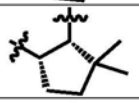
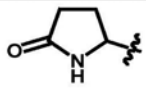
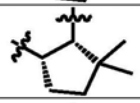
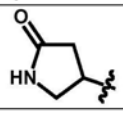
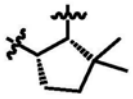
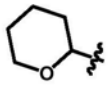
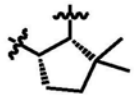
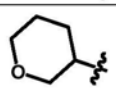
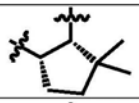
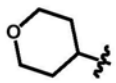
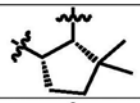
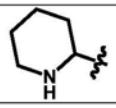
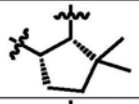
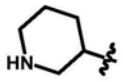
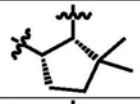
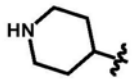
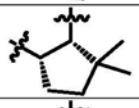
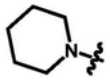
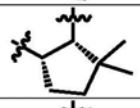
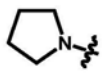
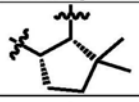
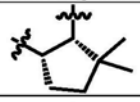
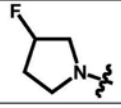
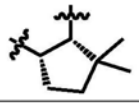
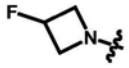
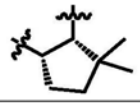
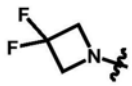
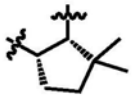
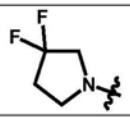
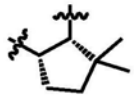
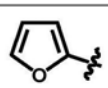
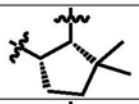
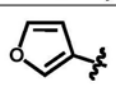
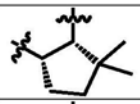
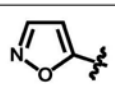
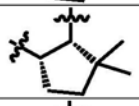
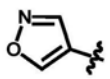
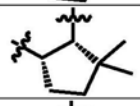
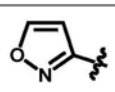
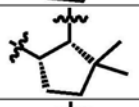
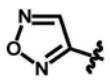
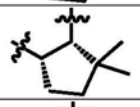
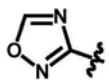
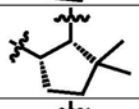
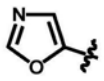
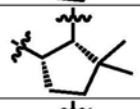
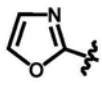
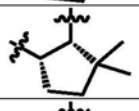
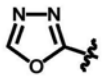
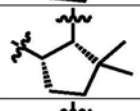
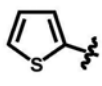
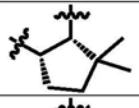
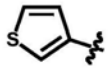
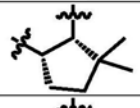
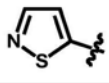
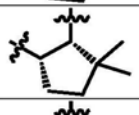
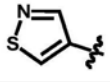
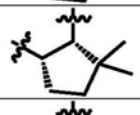
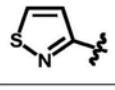
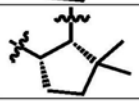
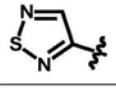
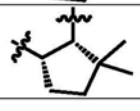
(X-6)

[0223] 表6

[0224]

化合物	R_2		化合物	R_2	
6-1			6-2		
6-3			6-4		
6-5			6-6		
6-7			6-8		

[0225]

6-9			6-10		
6-11			6-12		
6-13			6-14		
6-15			6-16		
6-17			6-18		
6-19			6-20		
6-21			6-22		
6-23			6-24		
6-25			6-26		
6-27			6-28		
6-29			6-30		
6-31			6-32		
6-33			6-34		
6-35			6-36		
6-37			6-38		
6-39			6-40		
6-41			6-42		

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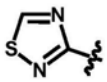
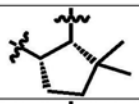
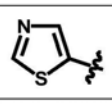
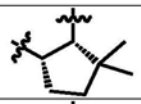
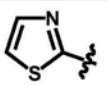
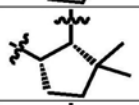
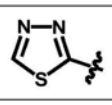
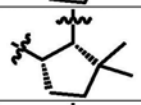
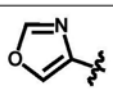
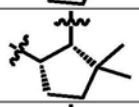
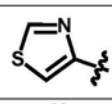
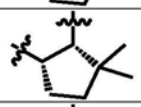
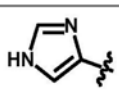
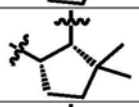
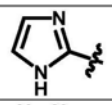
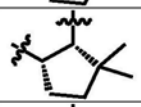
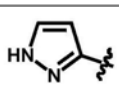
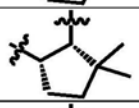
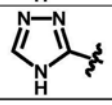
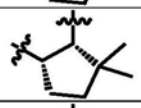
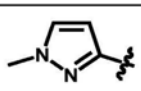
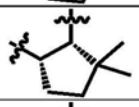
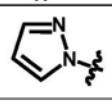
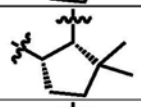
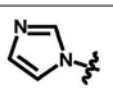
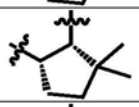
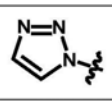
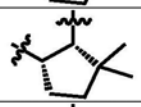
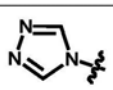
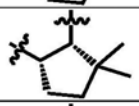
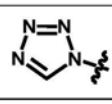
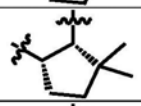
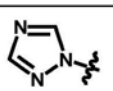
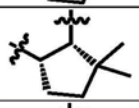
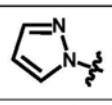
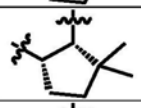
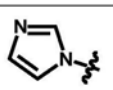
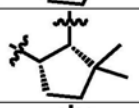
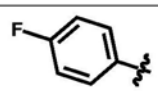
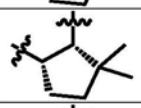
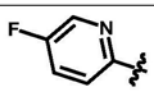
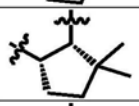
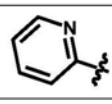
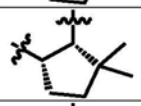
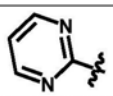
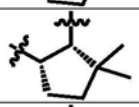
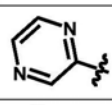
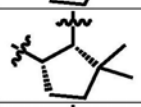
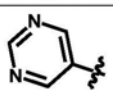
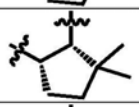
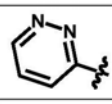
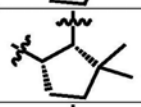
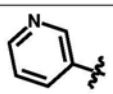
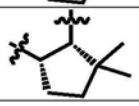
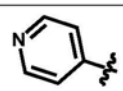
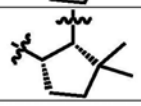
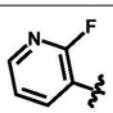
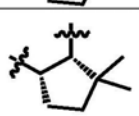
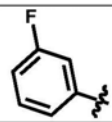
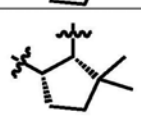
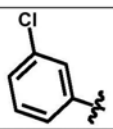
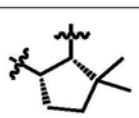
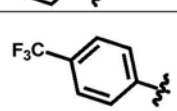
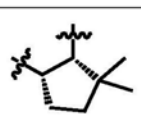
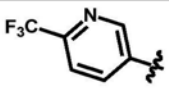
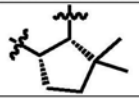
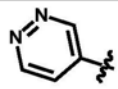
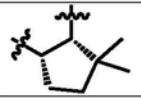
6-43			6-44		
6-45			6-46		
6-47			6-48		
6-49			6-50		
6-51			6-52		
6-53			6-54		
6-55			6-56		
6-57			6-58		
6-59			6-60		
6-61			6-62		
6-63			6-64		
6-65			6-66		
6-67			6-68		
6-69			6-70		
6-71			6-72		
6-73			6-74		
6-75			6-76		

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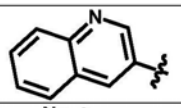
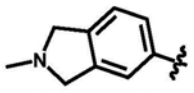
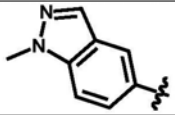
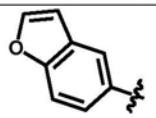
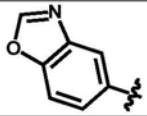
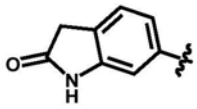
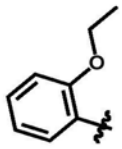
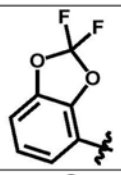
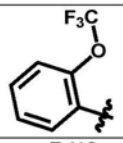
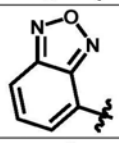
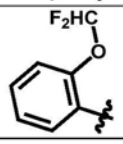
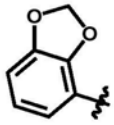
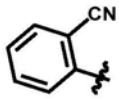
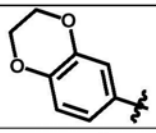
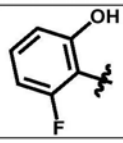
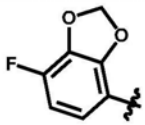
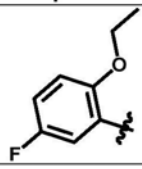
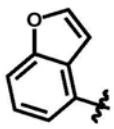
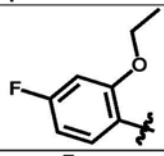
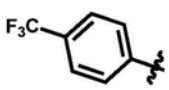
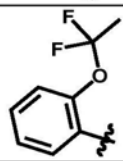
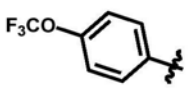
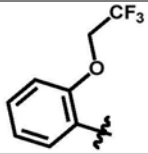
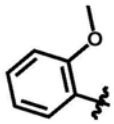
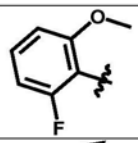
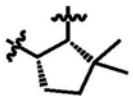
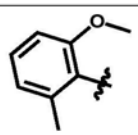
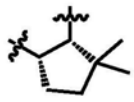
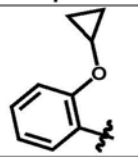
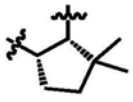
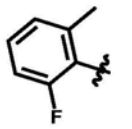
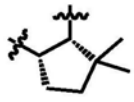
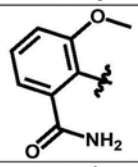
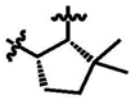
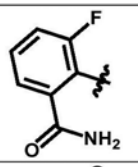
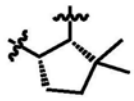
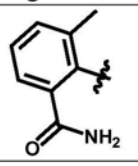
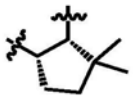
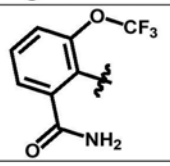
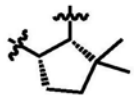
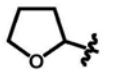
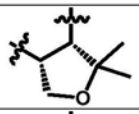
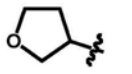
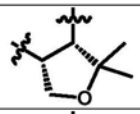
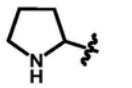
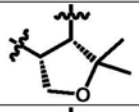
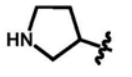
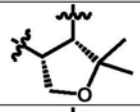
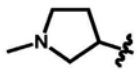
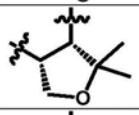
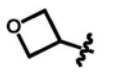
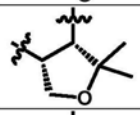
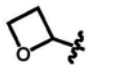
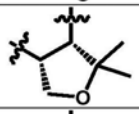
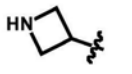
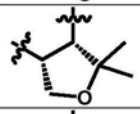
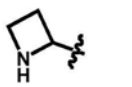
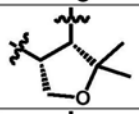
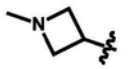
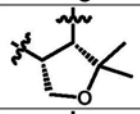
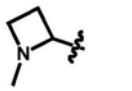
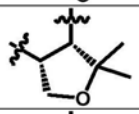
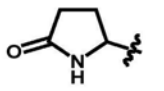
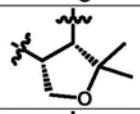
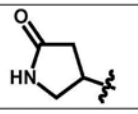
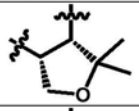
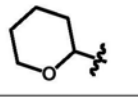
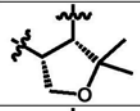
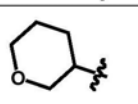
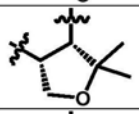
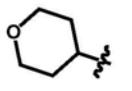
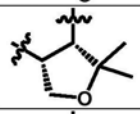
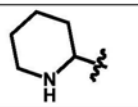
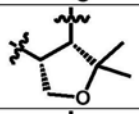
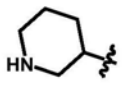
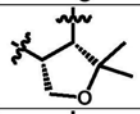
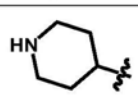
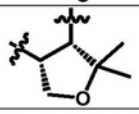
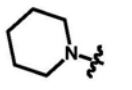
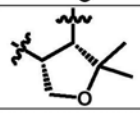
6-77			6-78		
6-79			6-80		
6-81			6-82		
6-83			6-84		
6-85			6-86		
6-87			6-88		
6-89			6-90		
6-91			6-92		
6-93			6-94		
6-95			6-96		
6-97			6-98		
6-99			6-100		

[0228]

6-101			6-102		
6-103			6-104		
6-105			6-106		
6-107			6-108		
6-109			6-110		
6-111			6-112		
6-113			6-114		
6-115			6-116		
6-117			6-118		
6-119			6-120		
6-121			6-122		
6-123			6-124		
6-125			6-126		
6-127			6-128		

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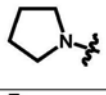
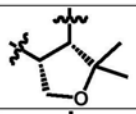
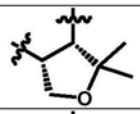
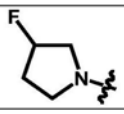
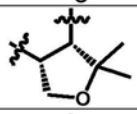
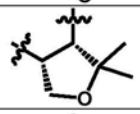
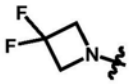
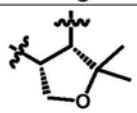
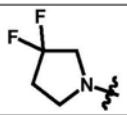
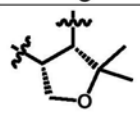
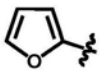
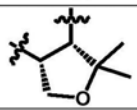
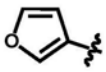
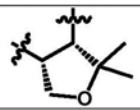
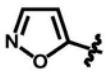
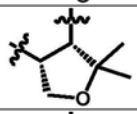
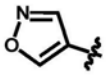
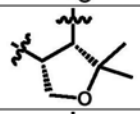
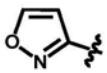
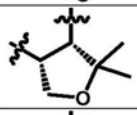
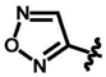
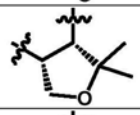
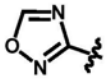
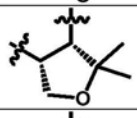
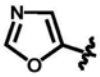
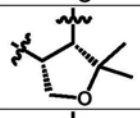
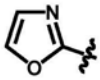
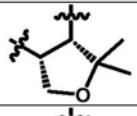
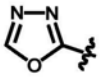
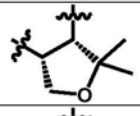
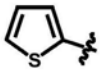
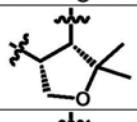
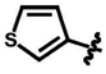
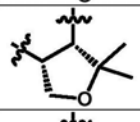
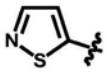
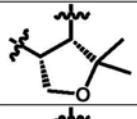
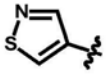
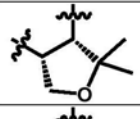
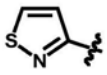
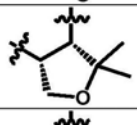
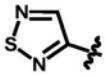
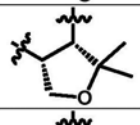
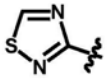
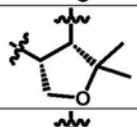
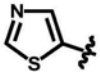
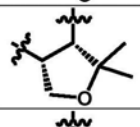
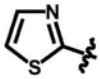
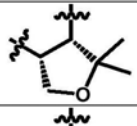
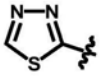
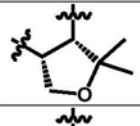
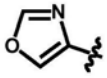
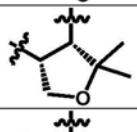
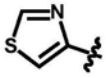
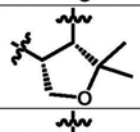
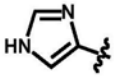
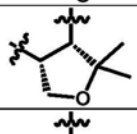
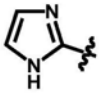
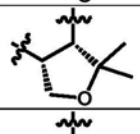
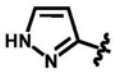
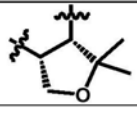
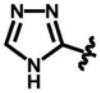
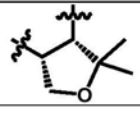
6-129			6-130		
6-131			6-132		
6-133			6-134		
6-135			6-136		
6-137			6-138		
6-139			6-140		
6-141			6-142		
6-143			6-144		
6-145			6-146		
6-147			6-148		
6-149			6-150		
6-151			6-152		
6-153			6-154		
6-155			6-156		
6-157			6-158		
6-159			6-160		

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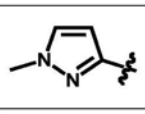
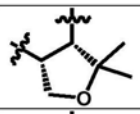
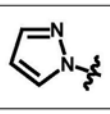
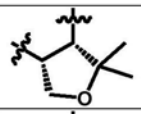
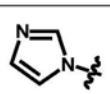
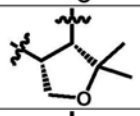
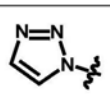
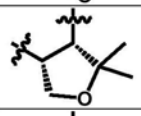
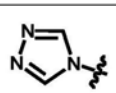
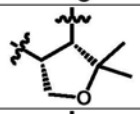
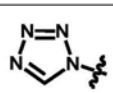
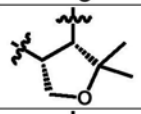
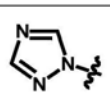
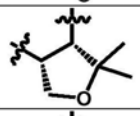
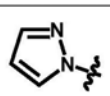
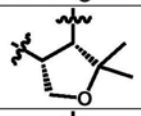
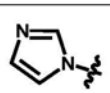
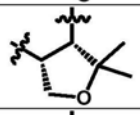
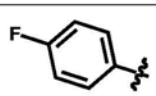
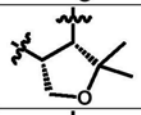
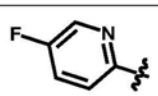
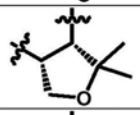
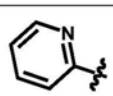
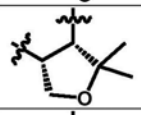
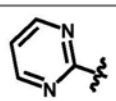
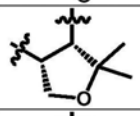
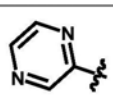
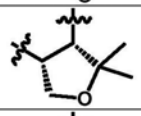
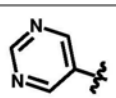
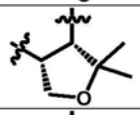
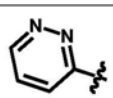
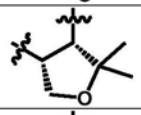
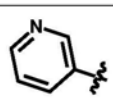
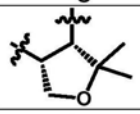
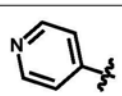
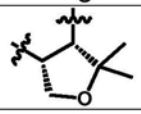
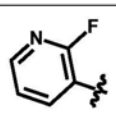
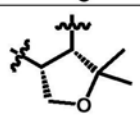
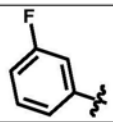
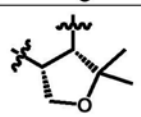
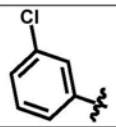
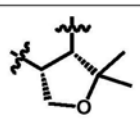
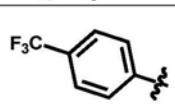
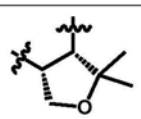
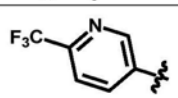
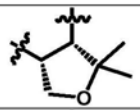
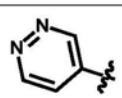
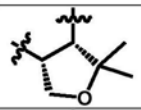
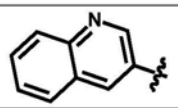
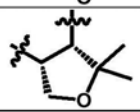
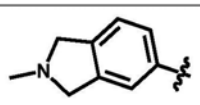
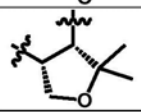
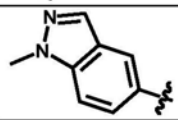
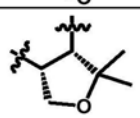
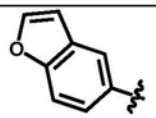
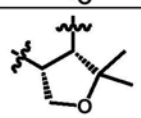
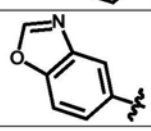
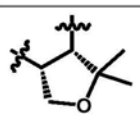
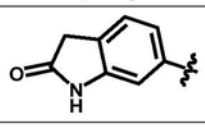
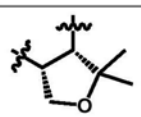
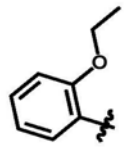
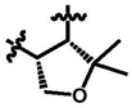
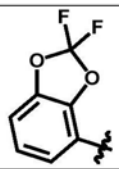
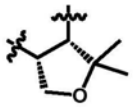
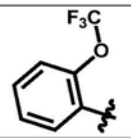
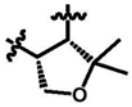
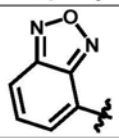
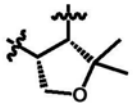
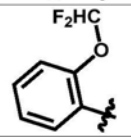
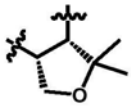
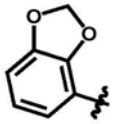
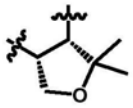
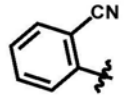
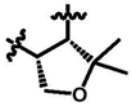
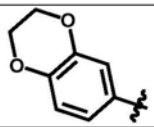
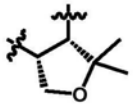
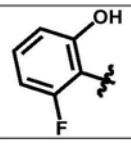
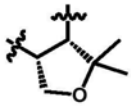
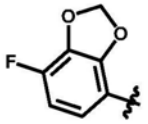
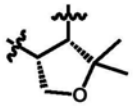
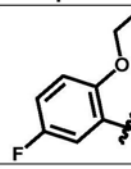
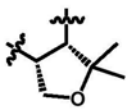
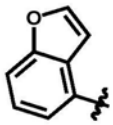
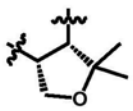
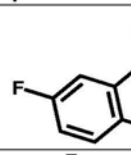
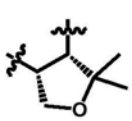
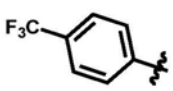
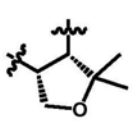
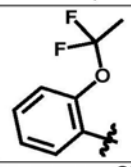
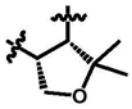
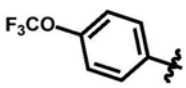
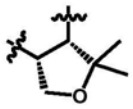
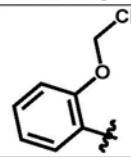
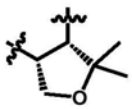
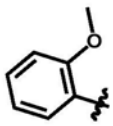
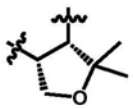
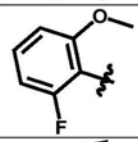
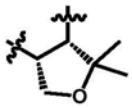
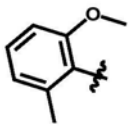
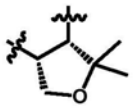
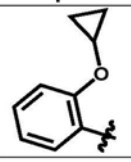
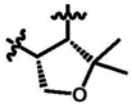
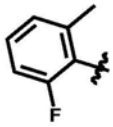
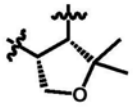
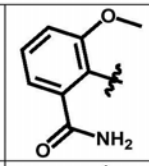
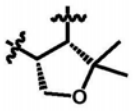
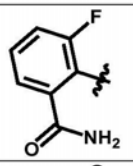
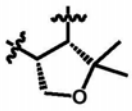
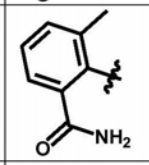
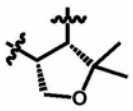
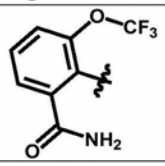
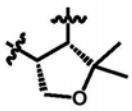
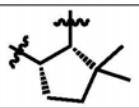
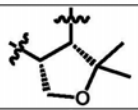
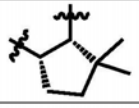
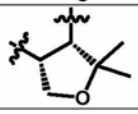
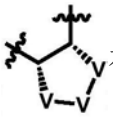
6-161			6-162		
6-163			6-164		
6-165			6-166		
6-167			6-168		
6-169			6-170		
6-171			6-172		
6-173			6-174		
6-175			6-176		
6-177			6-178		
6-179			6-180		
6-181			6-182		
6-183			6-184		
6-185			6-186		
6-187			6-188		
6-189			6-190		

[0231]

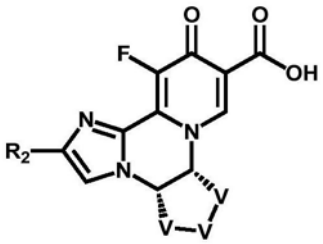
6-191			6-192		
6-193			6-194		
6-195			6-196		
6-197			6-198		
6-199			6-200		
6-201			6-202		
6-203			6-204		
6-205			6-206		
6-207			6-208		
6-209			6-210		
6-211			6-212		

[0232]

6-213			6-214		
6-215			6-216		
6-217			6-218		
6-219			6-220		

[0233] 本发明的代表性化合物包括但不限于根据式(X-7)的化合物，及其药学上可接受的盐，其中每一种化合物的R_2和  在表7中定义。

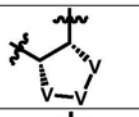
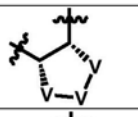
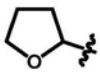
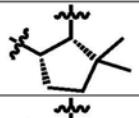
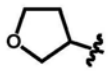
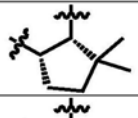
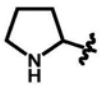
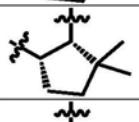
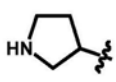
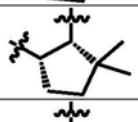
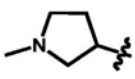
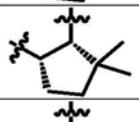
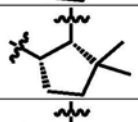
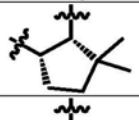
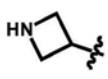
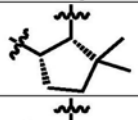
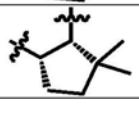
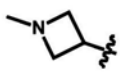
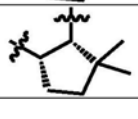
[0234]



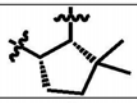
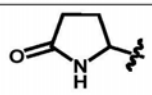
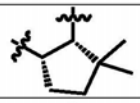
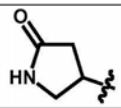
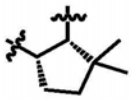
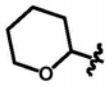
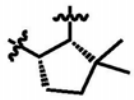
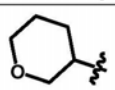
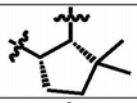
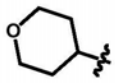
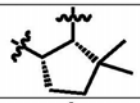
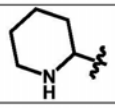
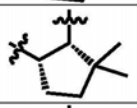
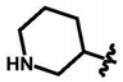
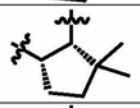
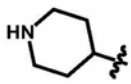
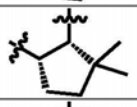
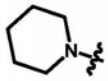
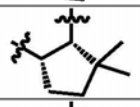
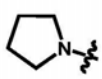
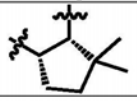
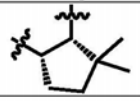
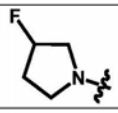
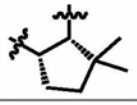
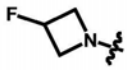
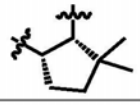
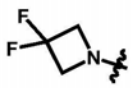
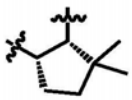
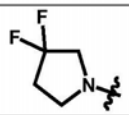
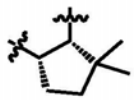
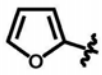
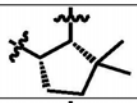
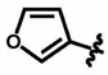
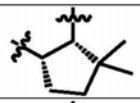
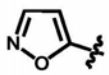
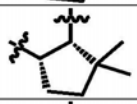
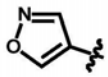
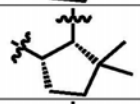
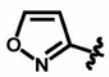
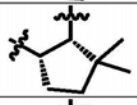
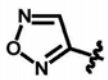
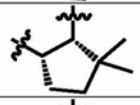
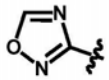
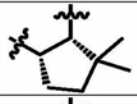
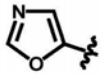
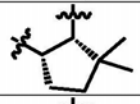
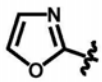
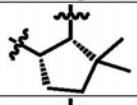
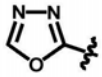
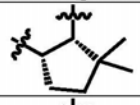
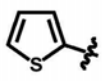
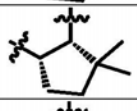
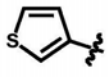
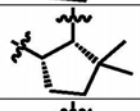
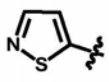
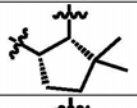
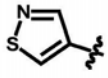
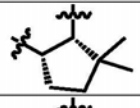
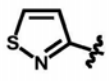
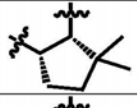
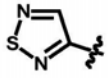
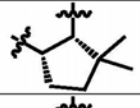
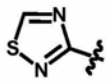
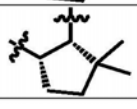
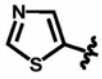
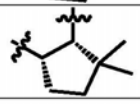
(X-7)

[0235] 表7

[0236]

化合物	R_2		化合物	R_2	
7-1			7-2		
7-3			7-4		
7-5			7-6		
7-7			7-8		
7-9			7-10		

[0237]

7-11			7-12		
7-13			7-14		
7-15			7-16		
7-17			7-18		
7-19			7-20		
7-21			7-22		
7-23			7-24		
7-25			7-26		
7-27			7-28		
7-29			7-30		
7-31			7-32		
7-33			7-34		
7-35			7-36		
7-37			7-38		
7-39			7-40		
7-41			7-42		
7-43			7-44		

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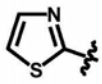
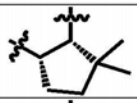
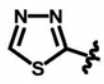
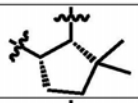
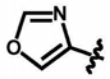
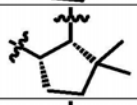
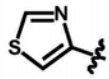
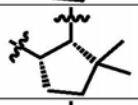
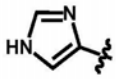
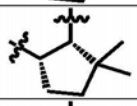
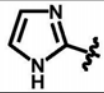
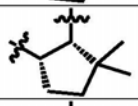
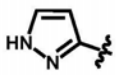
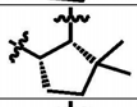
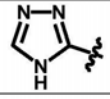
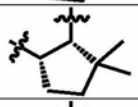
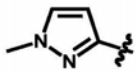
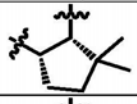
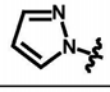
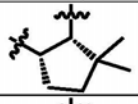
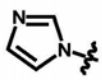
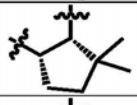
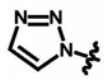
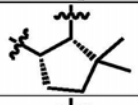
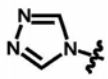
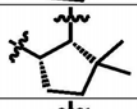
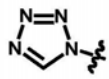
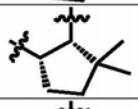
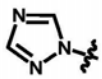
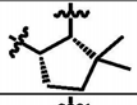
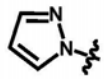
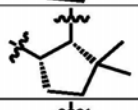
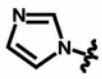
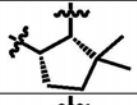
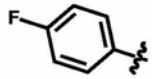
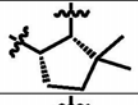
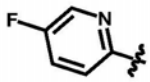
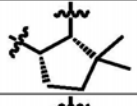
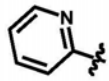
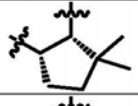
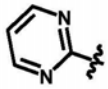
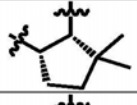
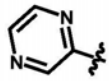
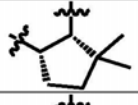
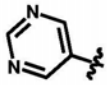
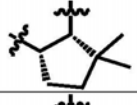
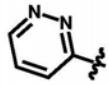
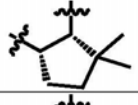
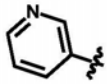
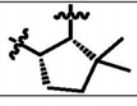
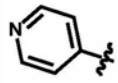
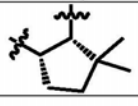
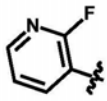
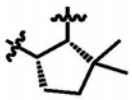
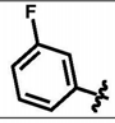
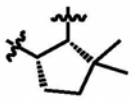
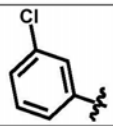
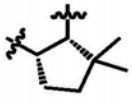
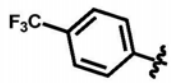
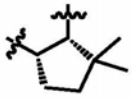
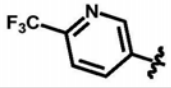
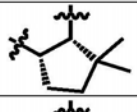
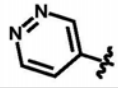
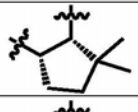
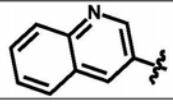
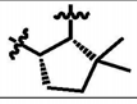
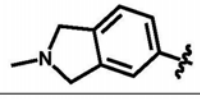
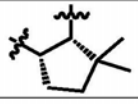
7-45			7-46		
7-47			7-48		
7-49			7-50		
7-51			7-52		
7-53			7-54		
7-55			7-56		
7-57			7-58		
7-59			7-60		
7-61			7-62		
7-63			7-64		
7-65			7-66		
7-67			7-68		
7-69			7-70		
7-71			7-72		
7-73			7-74		
7-75			7-76		
7-77			7-78		

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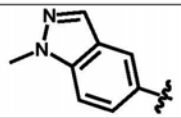
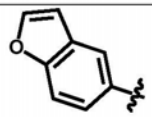
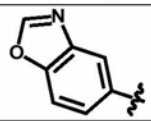
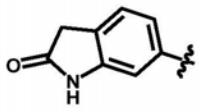
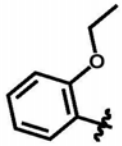
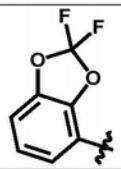
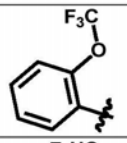
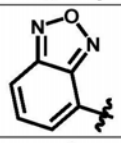
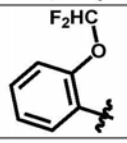
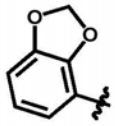
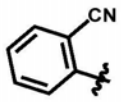
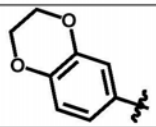
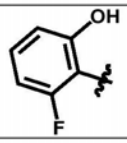
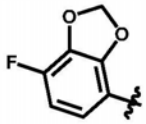
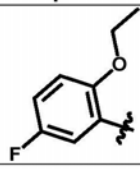
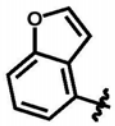
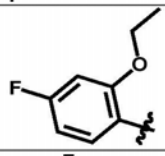
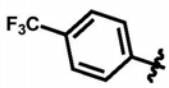
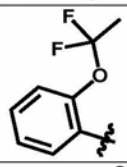
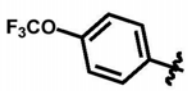
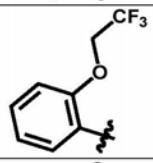
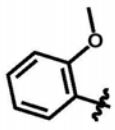
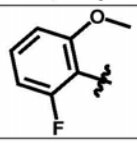
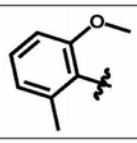
7-79			7-80		
7-81			7-82		
7-83			7-84		
7-85			7-86		
7-87			7-88		
7-89			7-90		
7-91			7-92		
7-93			7-94		
7-95			7-96		
7-97			7-98		
7-99			7-100		
7-101			7-102		

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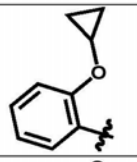
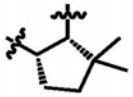
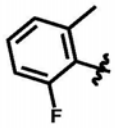
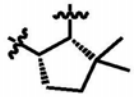
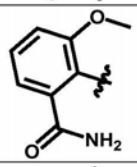
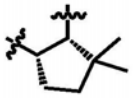
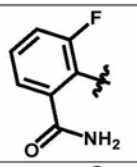
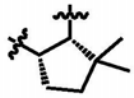
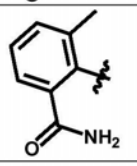
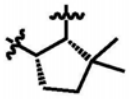
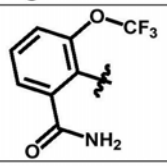
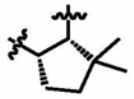
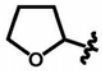
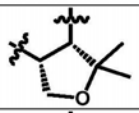
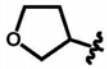
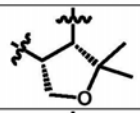
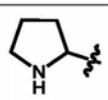
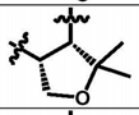
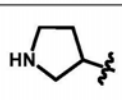
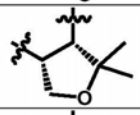
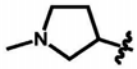
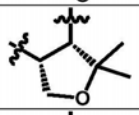
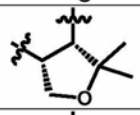
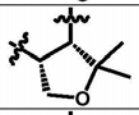
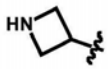
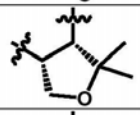
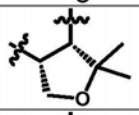
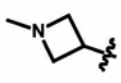
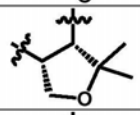
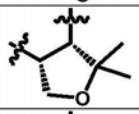
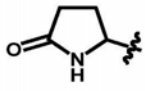
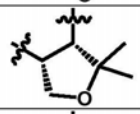
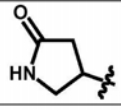
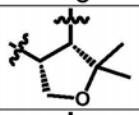
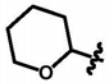
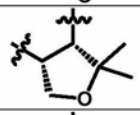
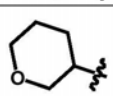
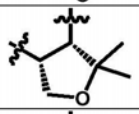
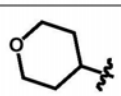
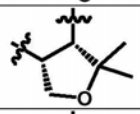
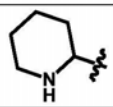
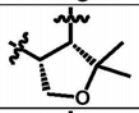
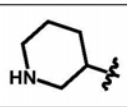
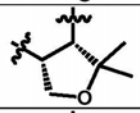
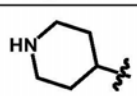
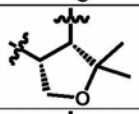
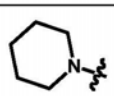
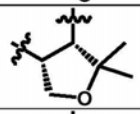
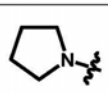
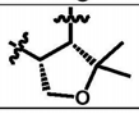
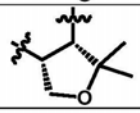
7-103			7-104		
7-105			7-106		
7-107			7-108		
7-109			7-110		
7-111			7-112		
7-113			7-114		
7-115			7-116		
7-117			7-118		
7-119			7-120		
7-121			7-122		
7-123			7-124		
7-125			7-126		
7-127			7-128		
7-129			7-130		

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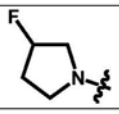
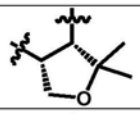
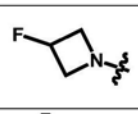
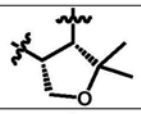
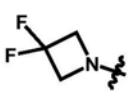
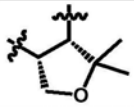
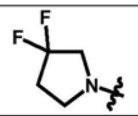
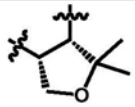
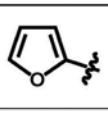
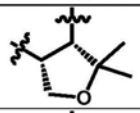
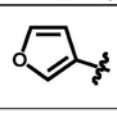
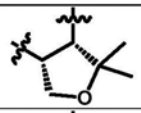
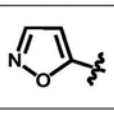
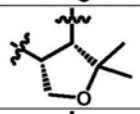
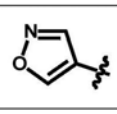
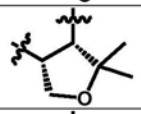
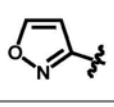
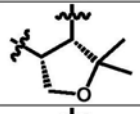
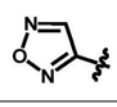
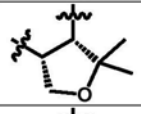
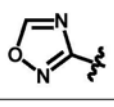
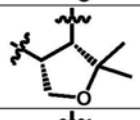
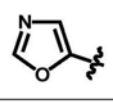
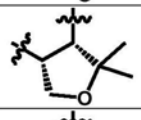
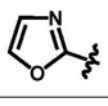
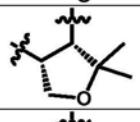
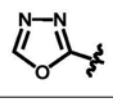
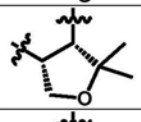
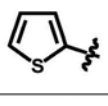
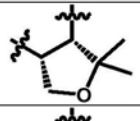
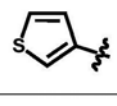
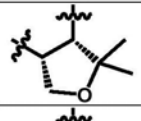
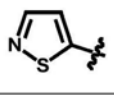
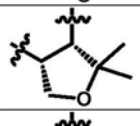
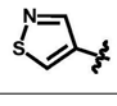
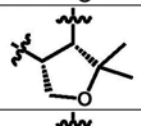
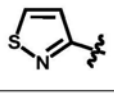
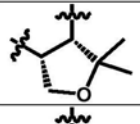
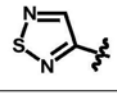
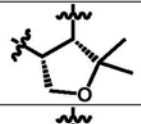
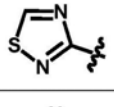
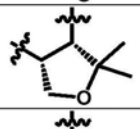
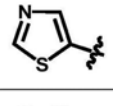
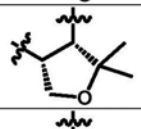
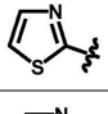
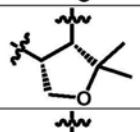
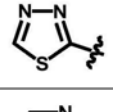
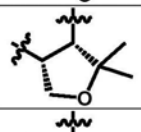
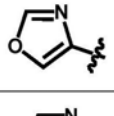
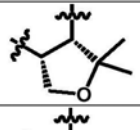
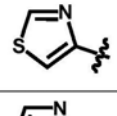
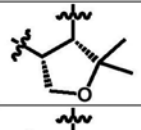
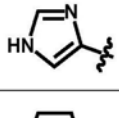
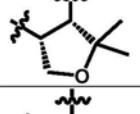
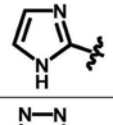
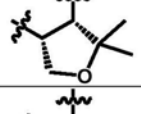
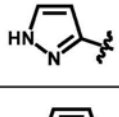
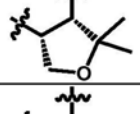
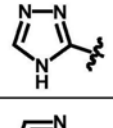
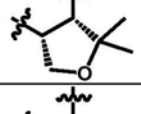
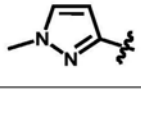
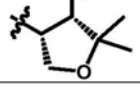
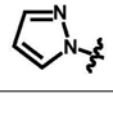
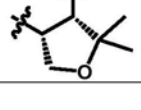
7-131			7-132		
7-133			7-134		
7-135			7-136		
7-137			7-138		
7-139			7-140		
7-141			7-142		
7-143			7-144		
7-145			7-146		
7-147			7-148		
7-149			7-150		
7-151			7-152		
7-153			7-154		
7-155			7-156		
7-157			7-158		
7-159			7-160		
7-161			7-162		

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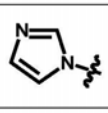
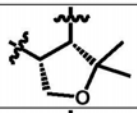
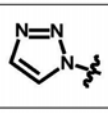
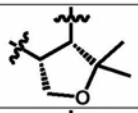
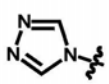
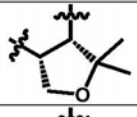
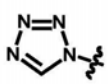
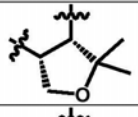
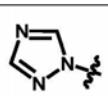
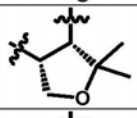
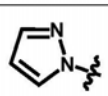
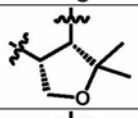
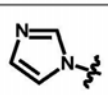
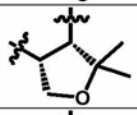
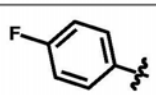
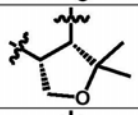
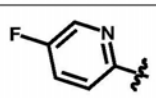
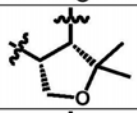
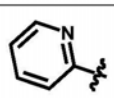
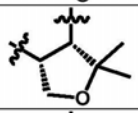
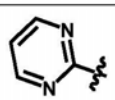
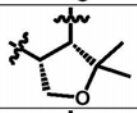
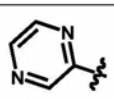
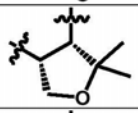
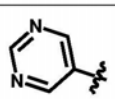
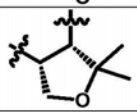
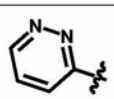
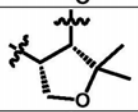
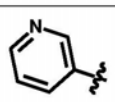
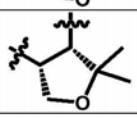
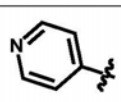
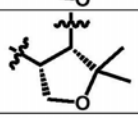
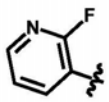
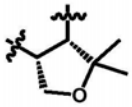
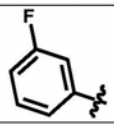
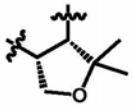
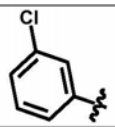
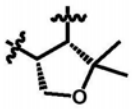
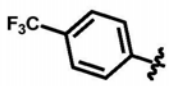
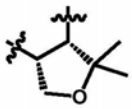
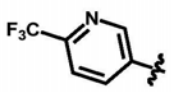
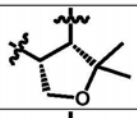
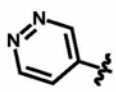
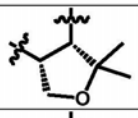
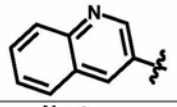
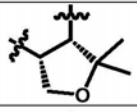
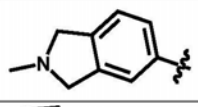
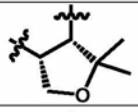
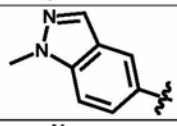
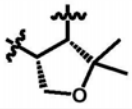
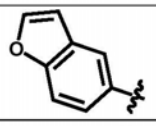
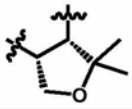
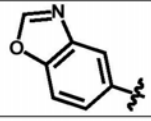
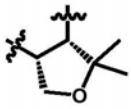
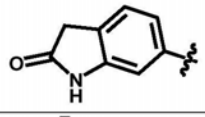
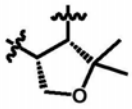
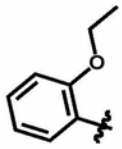
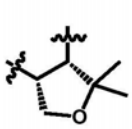
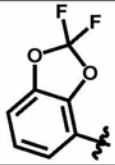
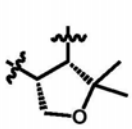
7-163			7-164		
7-165			7-166		
7-167			7-168		
7-169			7-170		
7-171			7-172		
7-173			7-174		
7-175			7-176		
7-177			7-178		
7-179			7-180		
7-181			7-182		
7-183			7-184		
7-185			7-186		
7-187			7-188		
7-189			7-190		
7-191			7-192		

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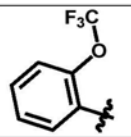
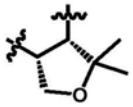
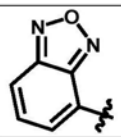
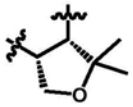
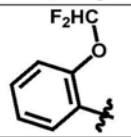
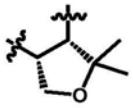
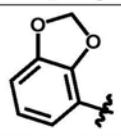
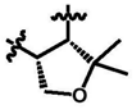
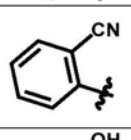
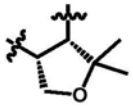
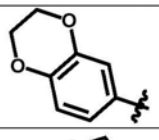
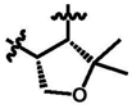
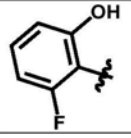
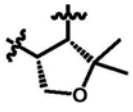
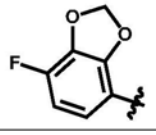
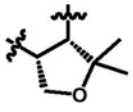
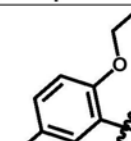
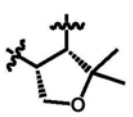
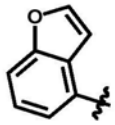
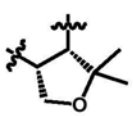
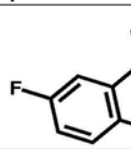
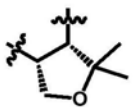
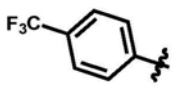
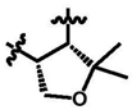
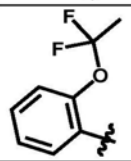
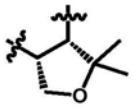
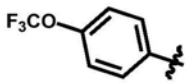
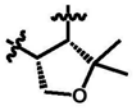
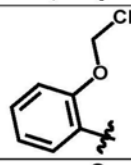
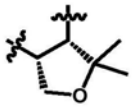
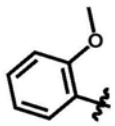
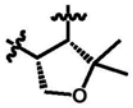
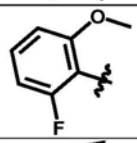
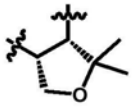
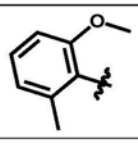
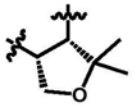
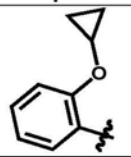
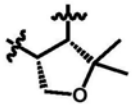
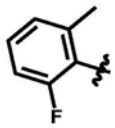
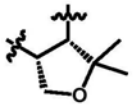
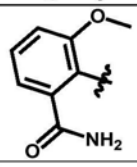
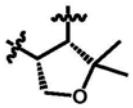
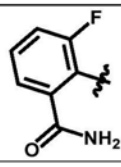
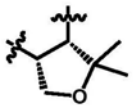
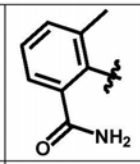
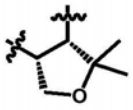
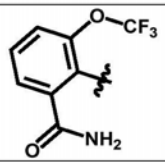
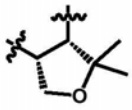
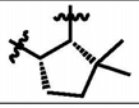
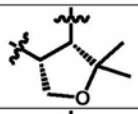
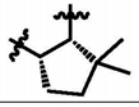
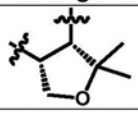
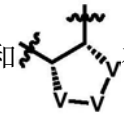
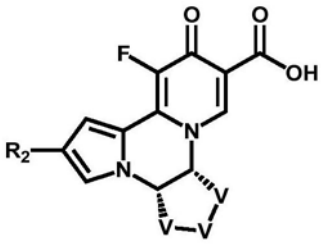
7-193			7-194		
7-195			7-196		
7-197			7-198		
7-199			7-200		
7-201			7-202		
7-203			7-204		
7-205			7-206		
7-207			7-208		
7-209			7-210		
7-211			7-212		
7-213			7-214		

[0244]

7-215			7-216		
7-217			7-218		
7-219			7-220		

[0245] 本发明的代表性化合物包括但不限于根据式(X-8)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2和  在表8中定义。

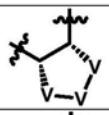
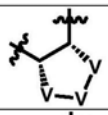
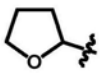
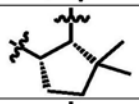
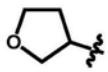
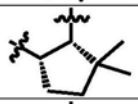
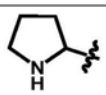
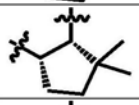
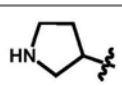
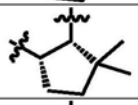
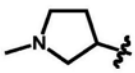
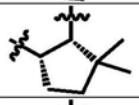
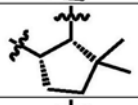
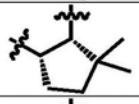
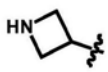
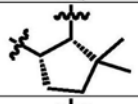
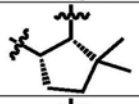
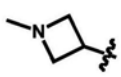
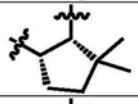
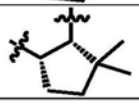
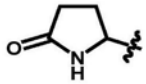
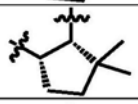
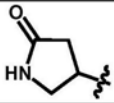
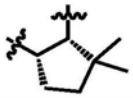
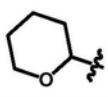
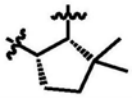
[0246]



(X-8)

[0247] 表8

[0248]

化合物	R_2		化合物	R_2	
8-1			8-2		
8-3			8-4		
8-5			8-6		
8-7			8-8		
8-9			8-10		
8-11			8-12		
8-13			8-14		

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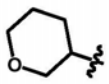
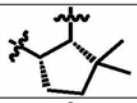
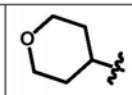
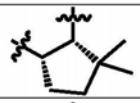
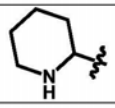
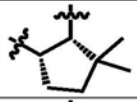
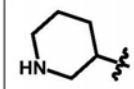
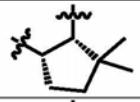
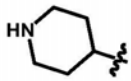
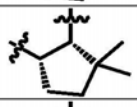
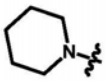
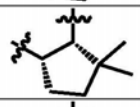
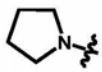
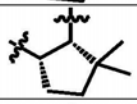
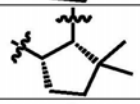
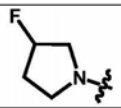
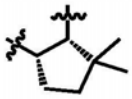
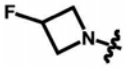
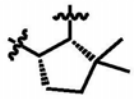
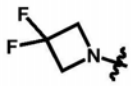
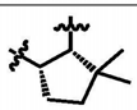
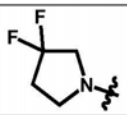
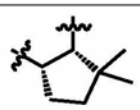
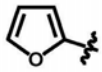
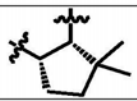
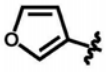
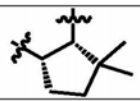
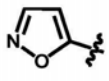
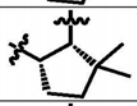
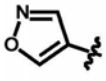
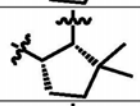
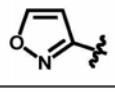
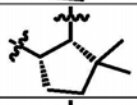
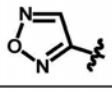
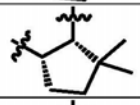
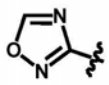
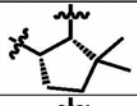
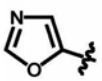
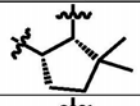
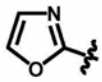
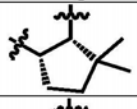
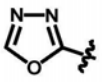
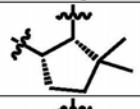
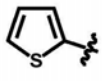
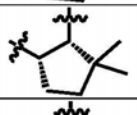
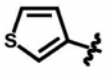
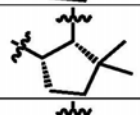
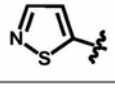
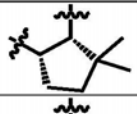
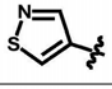
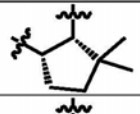
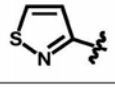
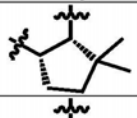
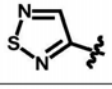
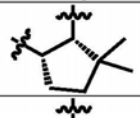
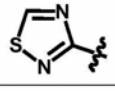
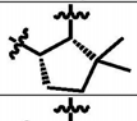
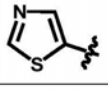
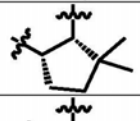
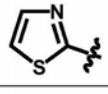
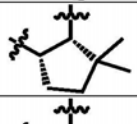
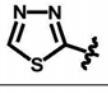
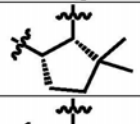
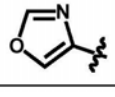
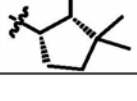
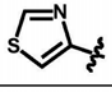
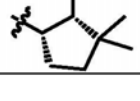
8-15			8-16		
8-17			8-18		
8-19			8-20		
8-21			8-22		
8-23			8-24		
8-25			8-26		
8-27			8-28		
8-29			8-30		
8-31			8-32		
8-33			8-34		
8-35			8-36		
8-37			8-38		
8-39			8-40		
8-41			8-42		
8-43			8-44		
8-45			8-46		
8-47			8-48		

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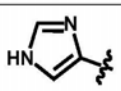
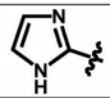
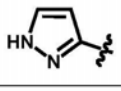
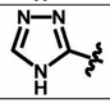
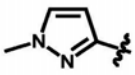
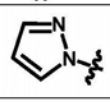
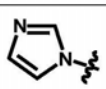
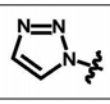
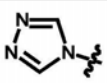
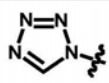
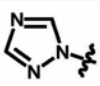
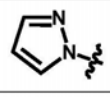
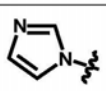
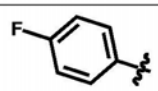
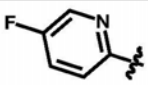
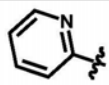
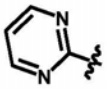
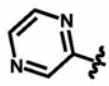
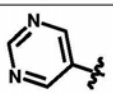
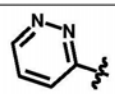
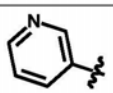
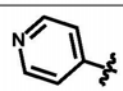
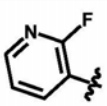
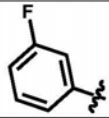
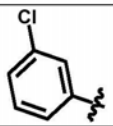
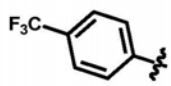
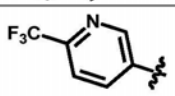
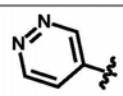
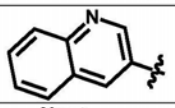
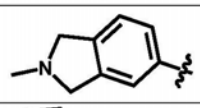
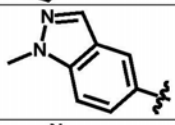
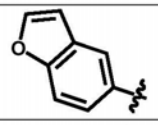
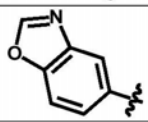
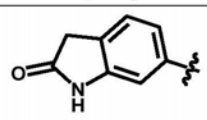
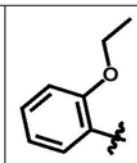
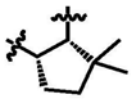
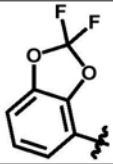
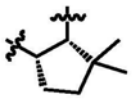
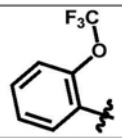
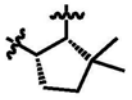
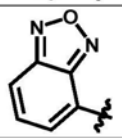
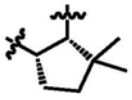
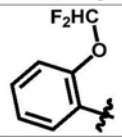
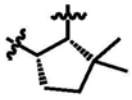
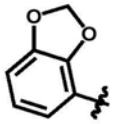
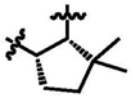
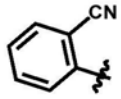
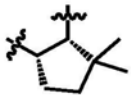
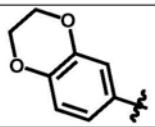
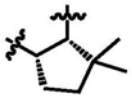
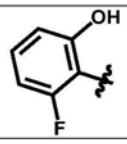
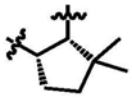
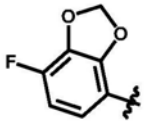
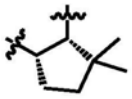
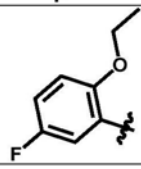
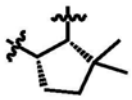
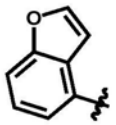
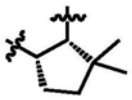
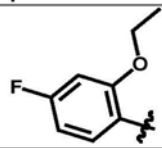
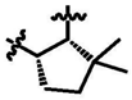
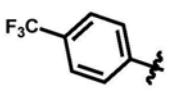
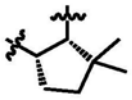
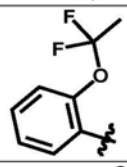
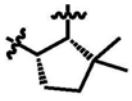
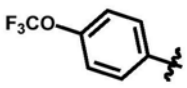
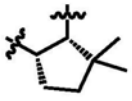
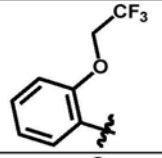
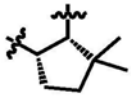
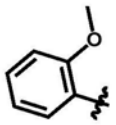
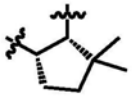
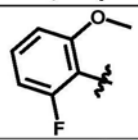
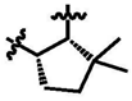
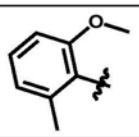
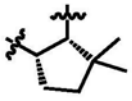
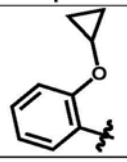
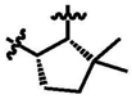
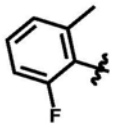
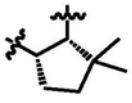
8-49			8-50		
8-51			8-52		
8-53			8-54		
8-55			8-56		
8-57			8-58		
8-59			8-60		
8-61			8-62		
8-63			8-64		
8-65			8-66		
8-67			8-68		
8-69			8-70		
8-71			8-72		
8-73			8-74		
8-75			8-76		
8-77			8-78		
8-79			8-80		
8-81			8-82		

[0251]

8-83			8-84		
8-85			8-86		
8-87			8-88		
8-89			8-90		
8-91			8-92		
8-93			8-94		
8-95			8-96		
8-97			8-98		
8-99			8-100		
8-101			8-102		
8-103			8-104		

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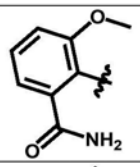
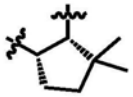
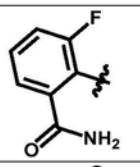
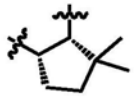
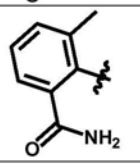
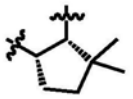
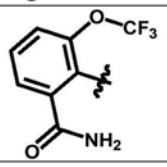
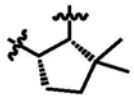
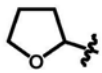
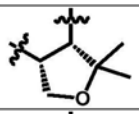
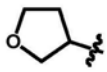
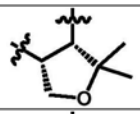
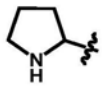
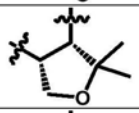
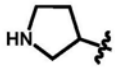
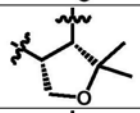
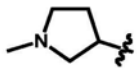
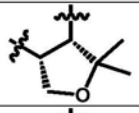
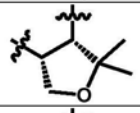
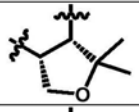
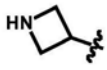
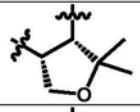
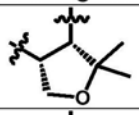
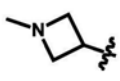
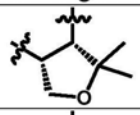
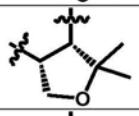
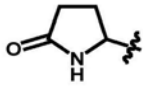
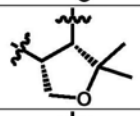
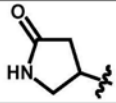
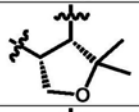
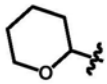
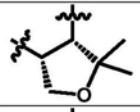
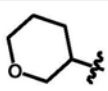
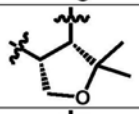
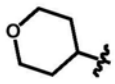
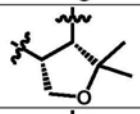
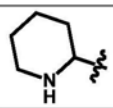
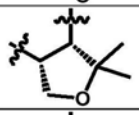
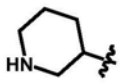
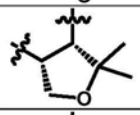
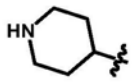
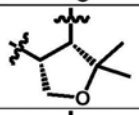
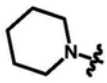
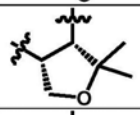
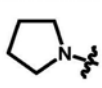
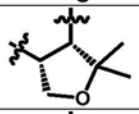
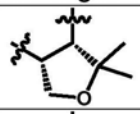
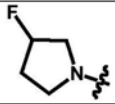
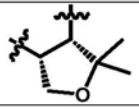
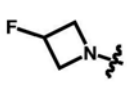
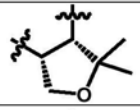
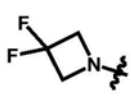
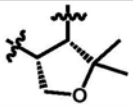
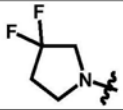
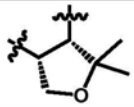
8-105			8-106		
8-107			8-108		
8-109			8-110		
8-111			8-112		
8-113			8-114		
8-115			8-116		
8-117			8-118		
8-119			8-120		
8-121			8-122		
8-123			8-124		
8-125			8-126		
8-127			8-128		
8-129			8-130		
8-131			8-132		
8-133			8-134		

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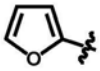
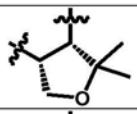
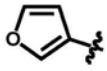
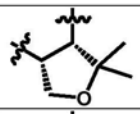
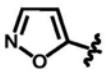
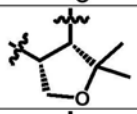
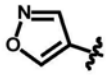
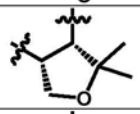
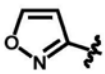
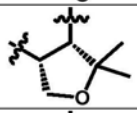
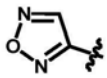
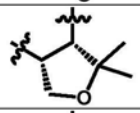
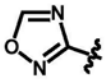
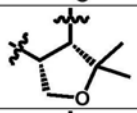
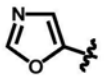
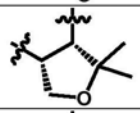
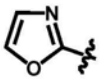
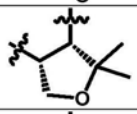
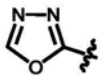
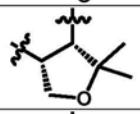
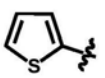
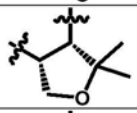
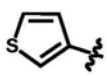
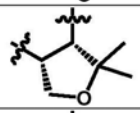
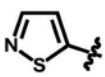
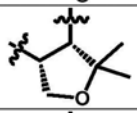
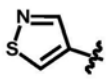
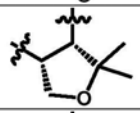
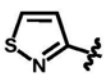
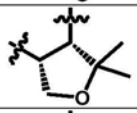
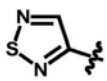
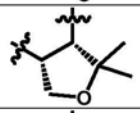
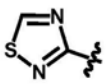
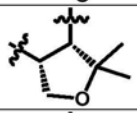
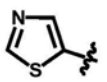
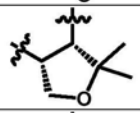
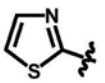
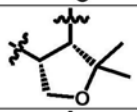
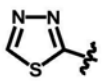
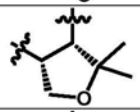
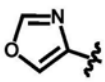
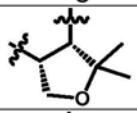
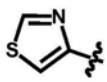
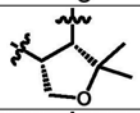
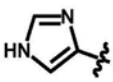
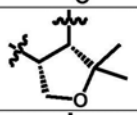
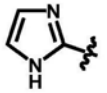
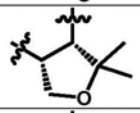
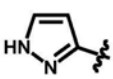
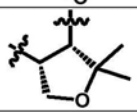
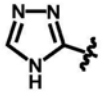
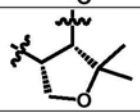
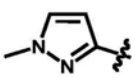
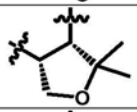
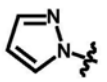
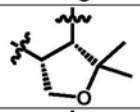
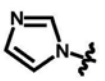
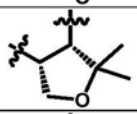
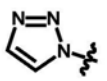
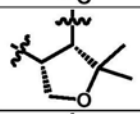
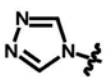
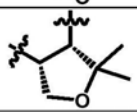
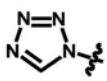
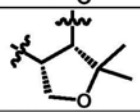
8-135			8-136		
8-137			8-138		
8-139			8-140		
8-141			8-142		
8-143			8-144		
8-145			8-146		
8-147			8-148		
8-149			8-150		
8-151			8-152		
8-153			8-154		
8-155			8-156		
8-157			8-158		
8-159			8-160		
8-161			8-162		
8-163			8-164		
8-165			8-166		

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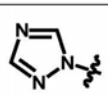
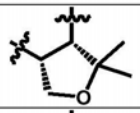
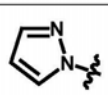
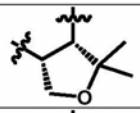
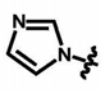
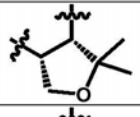
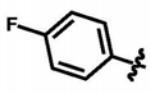
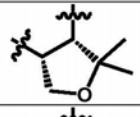
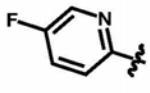
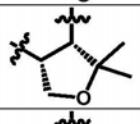
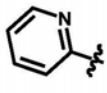
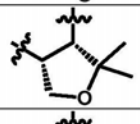
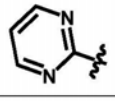
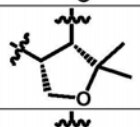
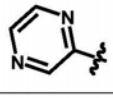
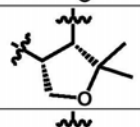
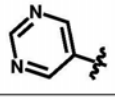
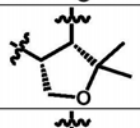
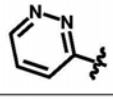
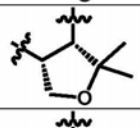
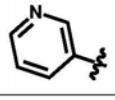
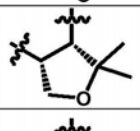
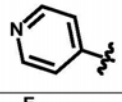
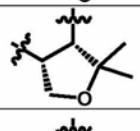
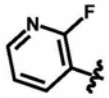
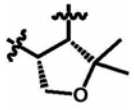
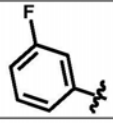
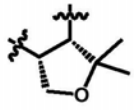
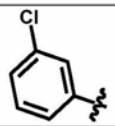
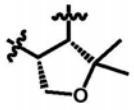
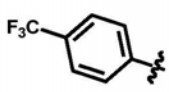
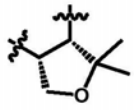
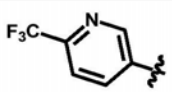
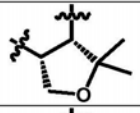
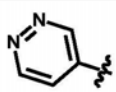
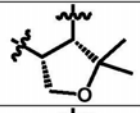
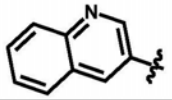
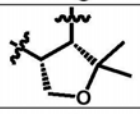
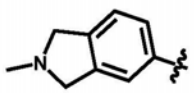
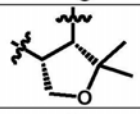
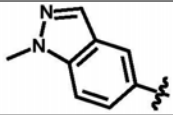
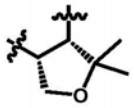
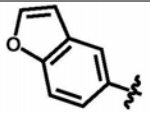
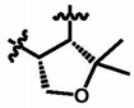
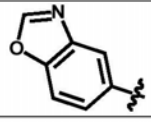
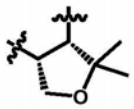
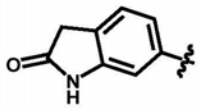
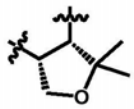
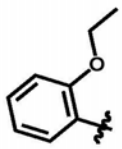
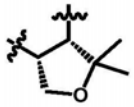
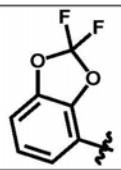
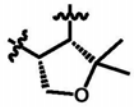
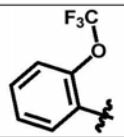
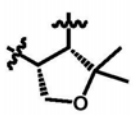
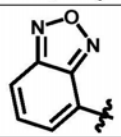
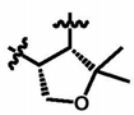
8-167			8-168		
8-169			8-170		
8-171			8-172		
8-173			8-174		
8-175			8-176		
8-177			8-178		
8-179			8-180		
8-181			8-182		
8-183			8-184		
8-185			8-186		
8-187			8-188		
8-189			8-190		
8-191			8-192		
8-193			8-194		

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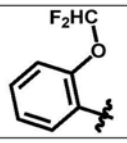
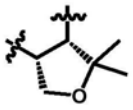
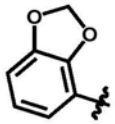
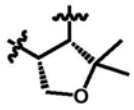
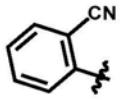
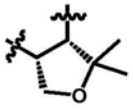
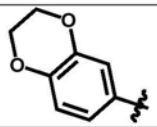
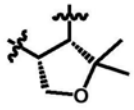
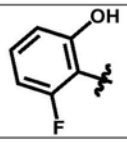
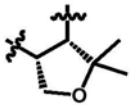
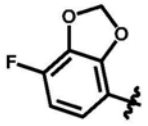
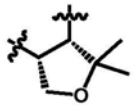
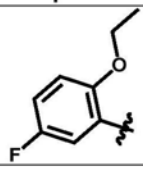
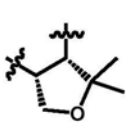
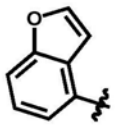
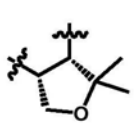
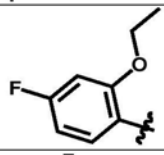
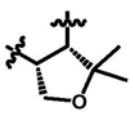
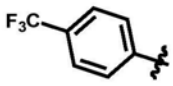
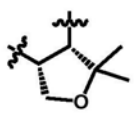
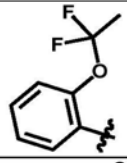
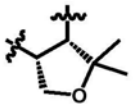
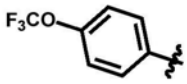
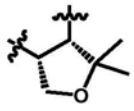
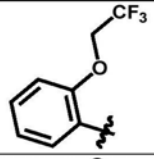
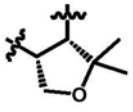
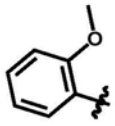
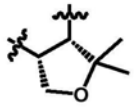
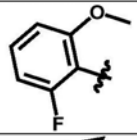
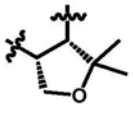
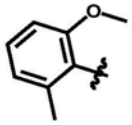
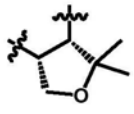
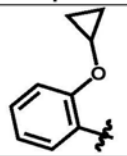
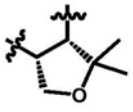
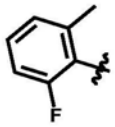
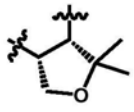
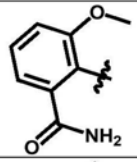
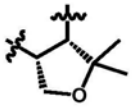
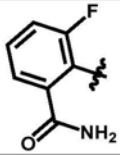
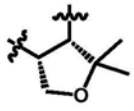
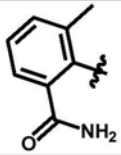
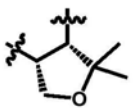
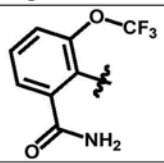
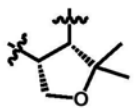
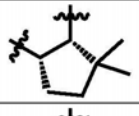
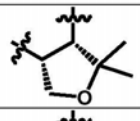
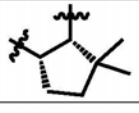
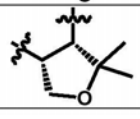
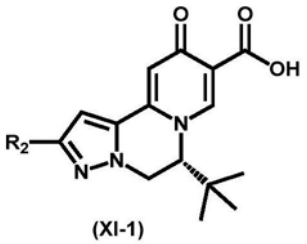
8-195			8-196		
8-197			8-198		
8-199			8-200		
8-201			8-202		
8-203			8-204		
8-205			8-206		
8-207			8-208		
8-209			8-210		
8-211			8-212		
8-213			8-214		
8-215			8-216		

[0256]

8-217			8-218		
8-219			8-220		

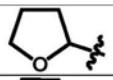
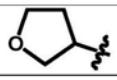
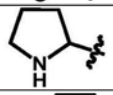
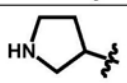
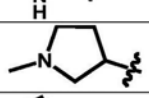
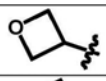
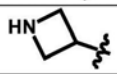
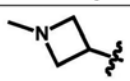
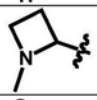
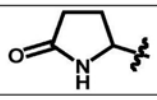
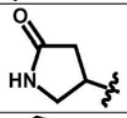
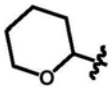
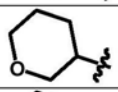
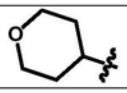
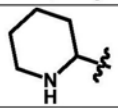
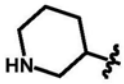
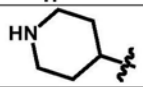
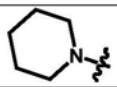
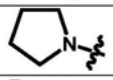
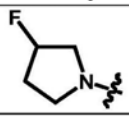
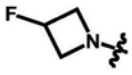
[0257] 本发明的代表性化合物包括但不限于根据式(XI-1)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表9中定义。

[0258] 

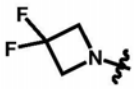
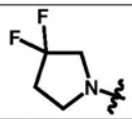
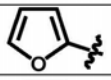
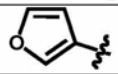
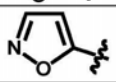
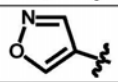
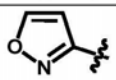
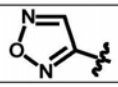
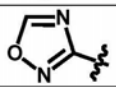
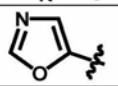
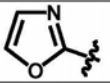
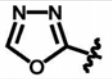
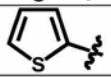
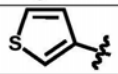
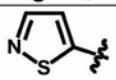
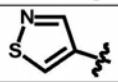
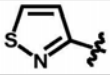
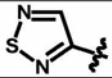
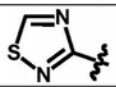
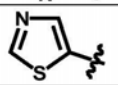
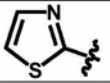
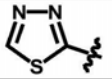
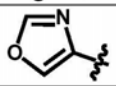
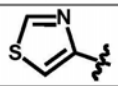
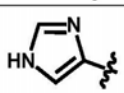
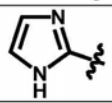
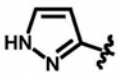
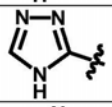
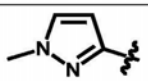
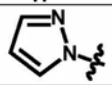
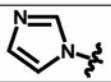
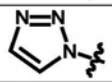
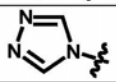
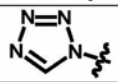
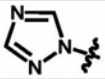
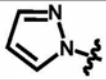
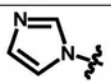
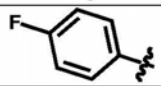
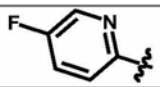
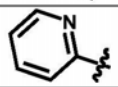
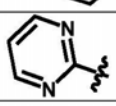
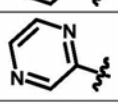
(XI-1)

[0259] 表9

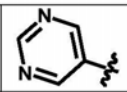
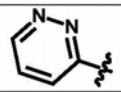
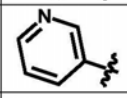
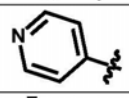
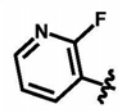
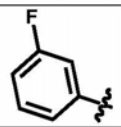
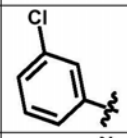
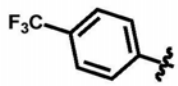
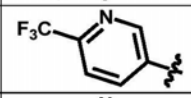
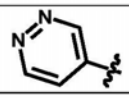
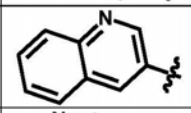
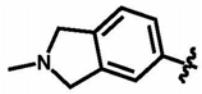
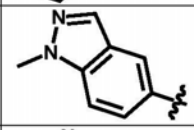
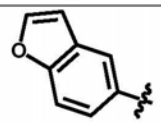
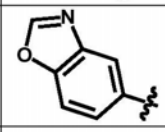
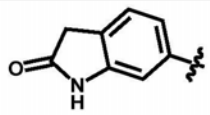
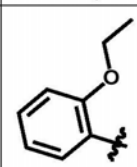
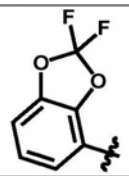
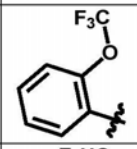
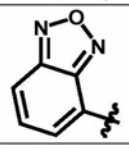
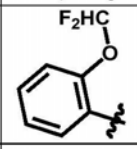
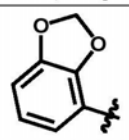
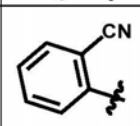
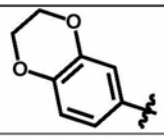
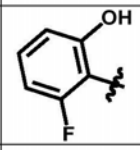
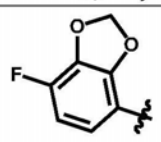
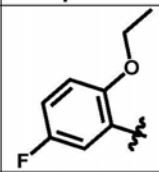
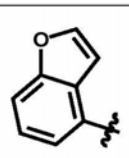
[0260]

化合物	R_2	化合物	R_2
9-1		9-2	
9-3		9-4	
9-5		9-6	
9-7		9-8	
9-9		9-10	
9-11		9-12	
9-13		9-14	
9-15		9-16	
9-17		9-18	
9-19		9-20	
9-21		9-22	
9-23		9-24	

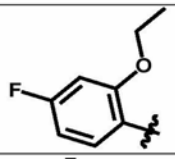
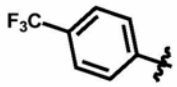
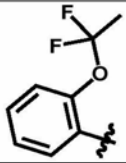
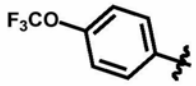
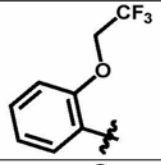
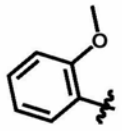
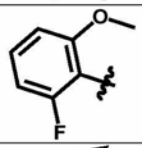
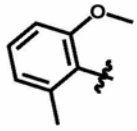
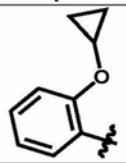
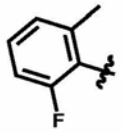
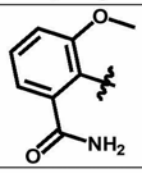
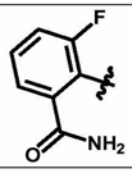
[0261]

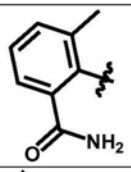
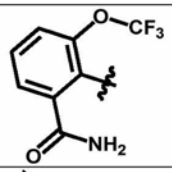
9-25		9-26	
9-27		9-28	
9-29		9-30	
9-31		9-32	
9-33		9-34	
9-35		9-36	
9-37		9-38	
9-39		9-40	
9-41		9-42	
9-43		9-44	
9-45		9-46	
9-47		9-48	
9-49		9-50	
9-51		9-52	
9-53		9-54	
9-55		9-56	
9-57		9-58	
9-59		9-60	
9-61		9-62	
9-63		9-64	
9-65		9-66	

[0262]

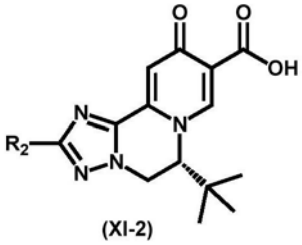
9-67		9-68	
9-69		9-70	
9-71		9-72	
9-73		9-74	
9-75		9-76	
9-77		9-78	
9-79		9-80	
9-81		9-82	
9-83		9-84	
9-85		9-86	
9-87		9-88	
9-89		9-90	
9-91		9-92	
9-93		9-94	

[0263]

9-95		9-96	
9-97		9-98	
9-99		9-100	
9-101		9-102	
9-103		9-104	
9-105		9-106	

9-107		9-108	
9-109		9-110	

[0264] 本发明的代表性化合物包括但不限于根据式(XI-2)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表10中定义。

[0265] 

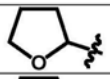
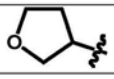
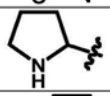
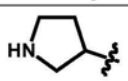
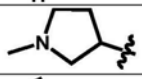
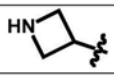
(XI-2)

[0266] 表10

[0267]

化合物	R_2	化合物	R_2

[0268]

10-1		10-2	
10-3		10-4	
10-5		10-6	
10-7		10-8	
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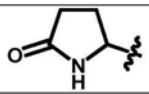
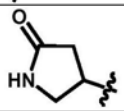
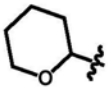
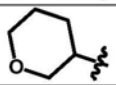
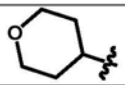
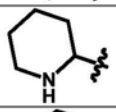
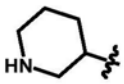
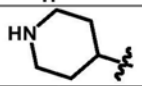
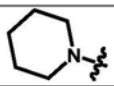
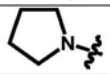
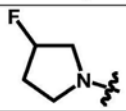
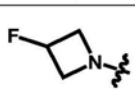
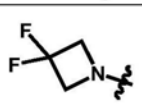
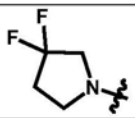
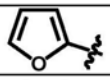
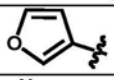
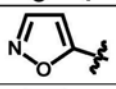
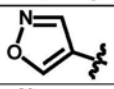
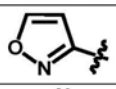
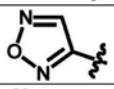
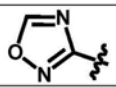
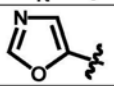
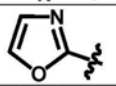
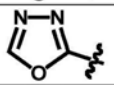
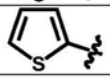
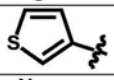
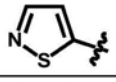
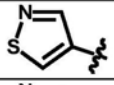
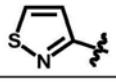
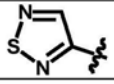
10-11		10-12	
10-13		10-14	
10-15		10-16	
10-17		10-18	
10-19		10-20	
10-21		10-22	
10-23		10-24	
10-25		10-26	
10-27		10-28	
10-29		10-30	
10-31		10-32	
10-33		10-34	
10-35		10-36	
10-37		10-38	
10-39		10-40	
10-41		10-42	

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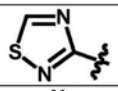
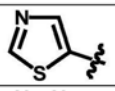
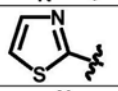
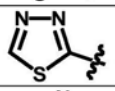
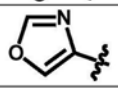
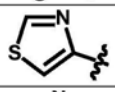
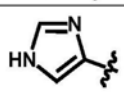
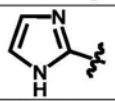
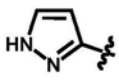
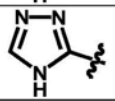
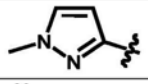
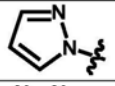
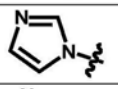
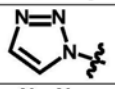
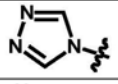
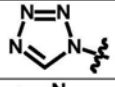
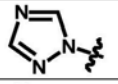
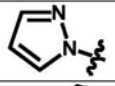
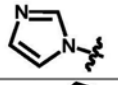
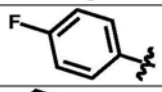
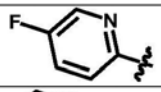
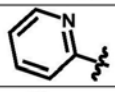
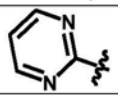
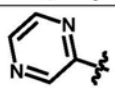
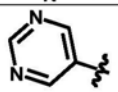
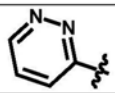
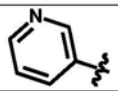
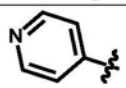
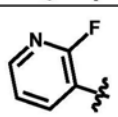
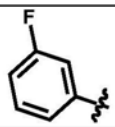
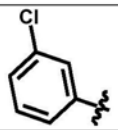
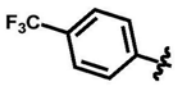
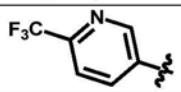
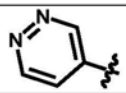
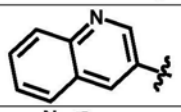
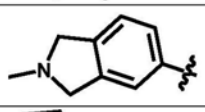
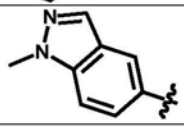
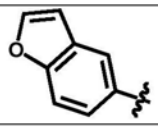
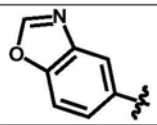
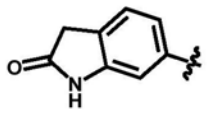
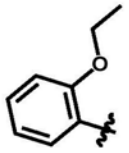
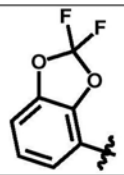
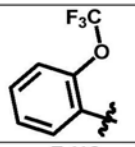
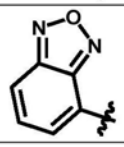
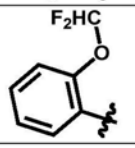
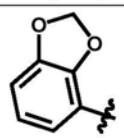
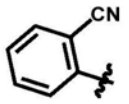
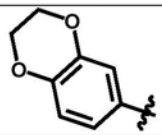
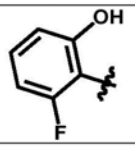
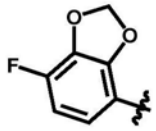
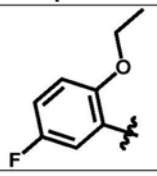
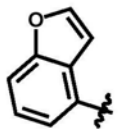
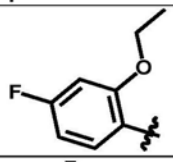
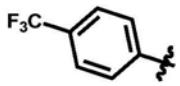
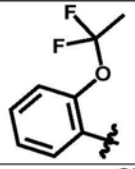
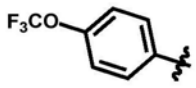
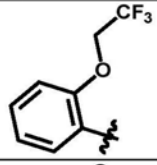
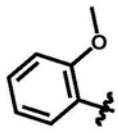
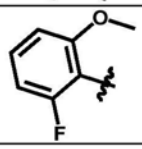
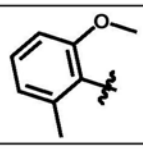
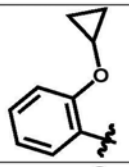
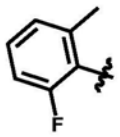
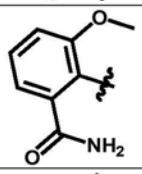
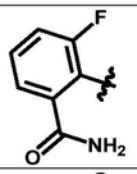
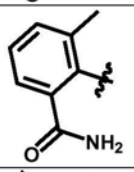
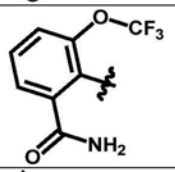
10-43		10-44	
10-45		10-46	
10-47		10-48	
10-49		10-50	
10-51		10-52	
10-53		10-54	
10-55		10-56	
10-57		10-58	
10-59		10-60	
10-61		10-62	
10-63		10-64	
10-65		10-66	
10-67		10-68	
10-69		10-70	
10-71		10-72	
10-73		10-74	
10-75		10-76	
10-77		10-78	
10-79		10-80	

[0270]

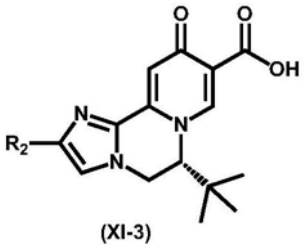
10-81		10-82	
10-83		10-84	
10-85		10-86	
10-87		10-88	
10-89		10-90	
10-91		10-92	
10-93		10-94	
10-95		10-96	
10-97		10-98	
10-99		10-100	
10-101		10-102	

[0271]

10-103		10-104	
10-105		10-106	
10-107		10-108	
10-109		10-110	

[0272] 本发明的代表性化合物包括但不限于根据式(XI-3)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表11中定义。

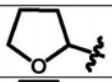
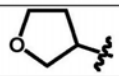
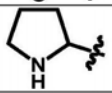
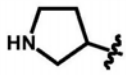
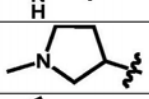
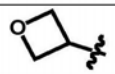
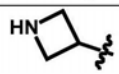
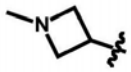
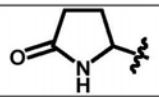
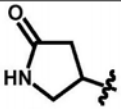
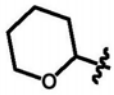
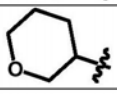
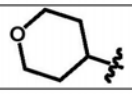
[0273]



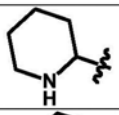
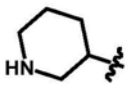
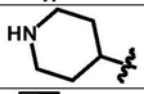
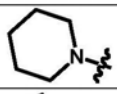
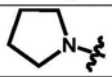
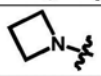
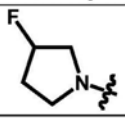
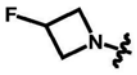
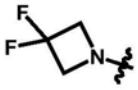
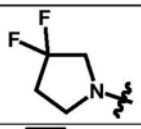
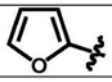
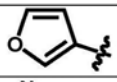
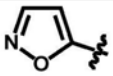
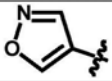
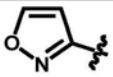
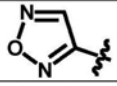
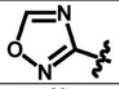
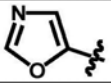
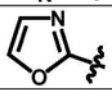
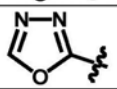
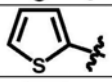
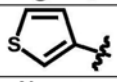
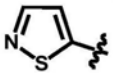
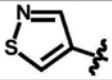
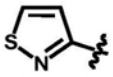
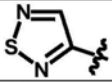
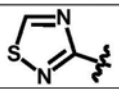
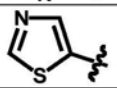
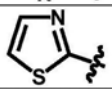
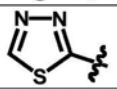
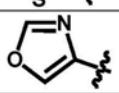
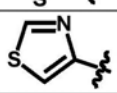
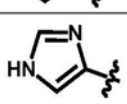
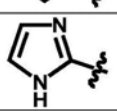
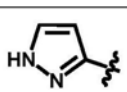
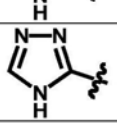
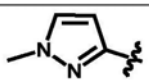
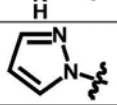
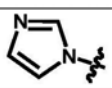
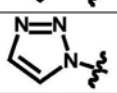
(XI-3)

[0274] 表11

[0275]

化合物	R_2	化合物	R_2
11-1		11-2	
11-3		11-4	
11-5		11-6	
11-7		11-8	
11-9		11-10	
11-11		11-12	
11-13		11-14	
11-15		11-16	

[0276]

11-17		11-18	
11-19		11-20	
11-21		11-22	
11-23		11-24	
11-25		11-26	
11-27		11-28	
11-29		11-30	
11-31		11-32	
11-33		11-34	
11-35		11-36	
11-37		11-38	
11-39		11-40	
11-41		11-42	
11-43		11-44	
11-45		11-46	
11-47		11-48	
11-49		11-50	
11-51		11-52	
11-53		11-54	
11-55		11-56	

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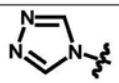
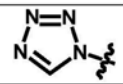
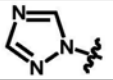
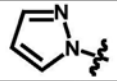
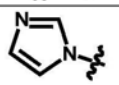
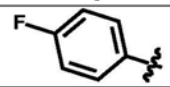
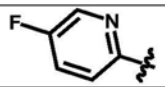
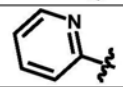
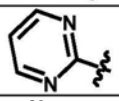
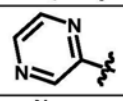
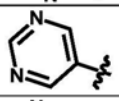
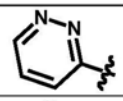
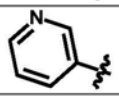
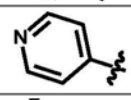
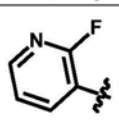
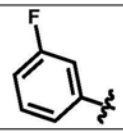
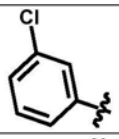
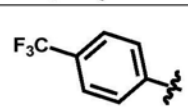
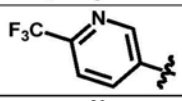
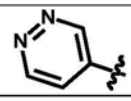
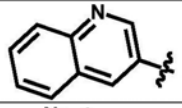
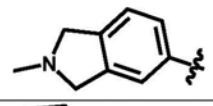
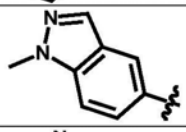
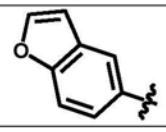
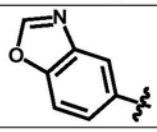
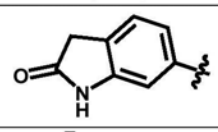
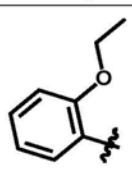
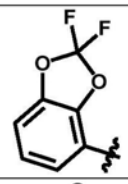
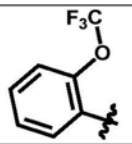
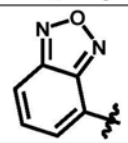
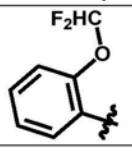
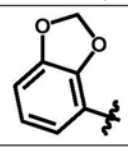
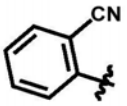
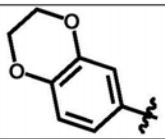
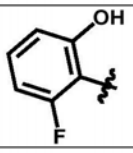
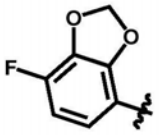
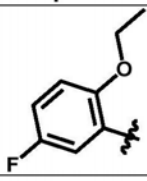
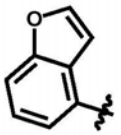
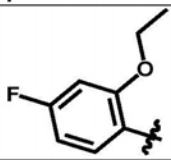
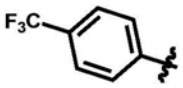
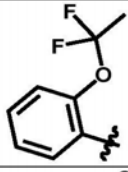
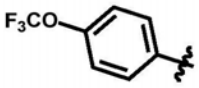
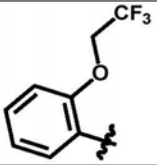
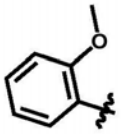
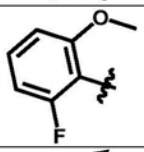
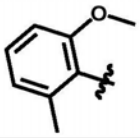
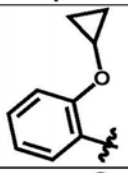
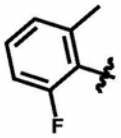
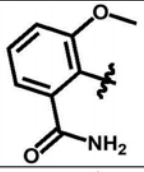
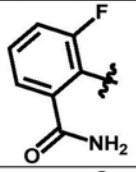
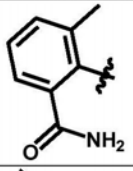
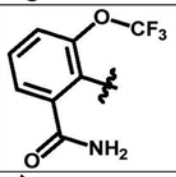
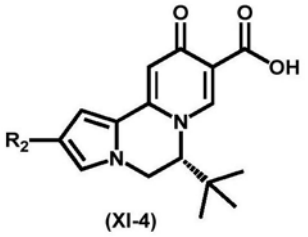
11-57		11-58	
11-59		11-60	
11-61		11-62	
11-63		11-64	
11-65		11-66	
11-67		11-68	
11-69		11-70	
11-71		11-72	
11-73		11-74	
11-75		11-76	
11-77		11-78	
11-79		11-80	
11-81		11-82	
11-83		11-84	
11-85		11-86	
11-87		11-88	

[0278]

11-89		11-90	
11-91		11-92	
11-93		11-94	
11-95		11-96	
11-97		11-98	
11-99		11-100	
11-101		11-102	
11-103		11-104	
11-105		11-106	
11-107		11-108	
11-109		11-110	

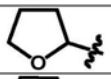
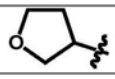
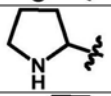
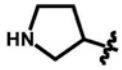
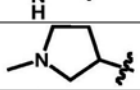
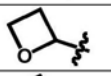
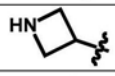
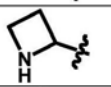
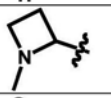
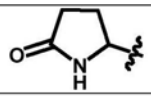
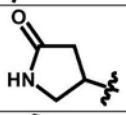
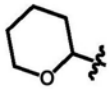
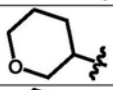
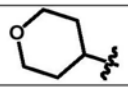
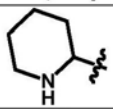
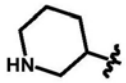
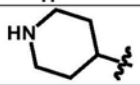
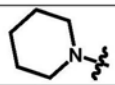
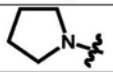
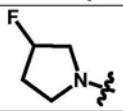
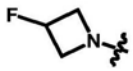
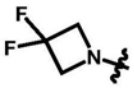
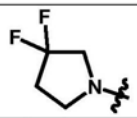
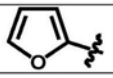
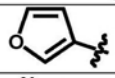
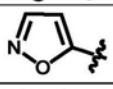
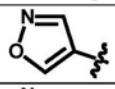
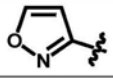
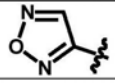
[0279] 本发明的代表性化合物包括但不限于根据式(XI-4)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表12中定义。

[0280] 

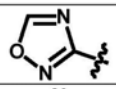
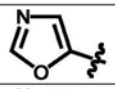
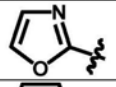
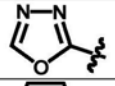
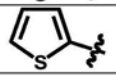
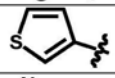
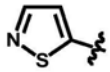
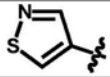
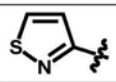
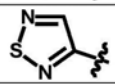
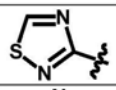
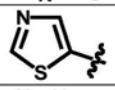
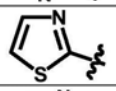
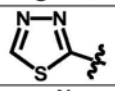
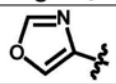
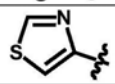
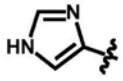
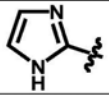
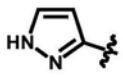
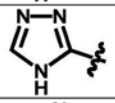
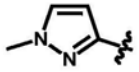
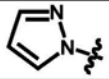
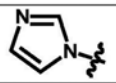
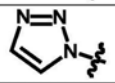
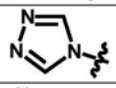
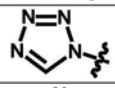
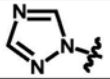
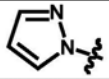
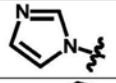
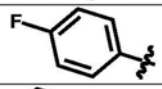
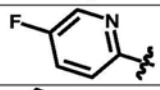
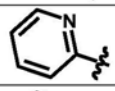
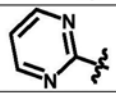
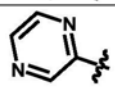
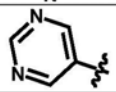
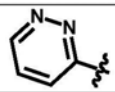
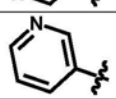
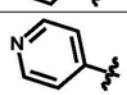
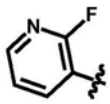
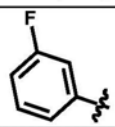
(XI-4)

[0281] 表12

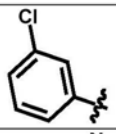
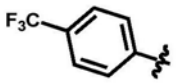
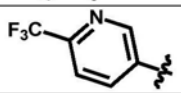
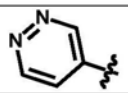
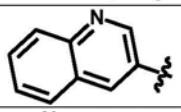
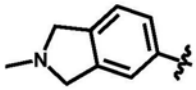
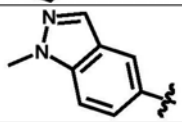
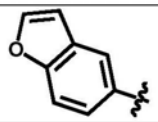
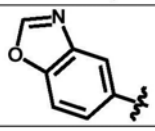
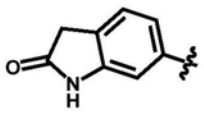
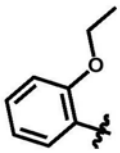
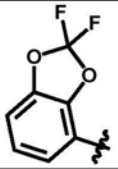
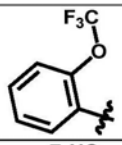
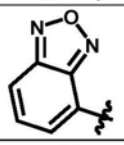
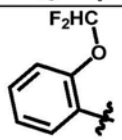
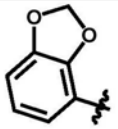
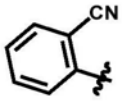
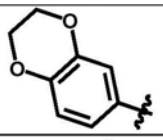
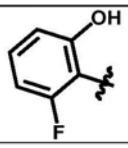
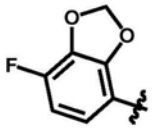
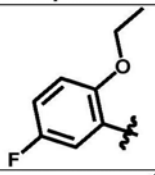
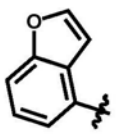
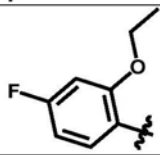
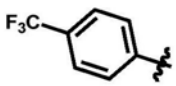
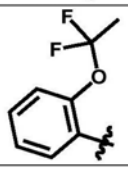
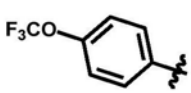
[0282]

化合物	R_2	化合物	R_2
12-1		12-2	
12-3		12-4	
12-5		12-6	
12-7		12-8	
12-9		12-10	
12-11		12-12	
12-13		12-14	
12-15		12-16	
12-17		12-18	
12-19		12-20	
12-21		12-22	
12-23		12-24	
12-25		12-26	
12-27		12-28	
12-29		12-30	
12-31		12-32	

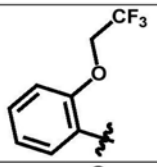
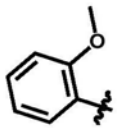
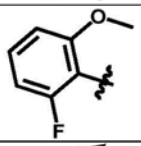
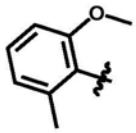
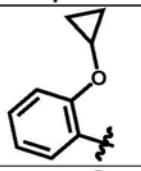
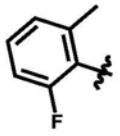
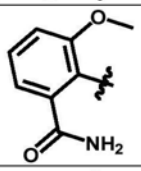
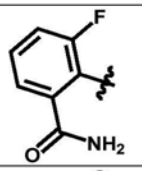
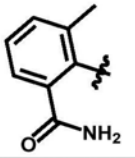
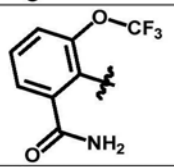
[0283]

12-33		12-34	
12-35		12-36	
12-37		12-38	
12-39		12-40	
12-41		12-42	
12-43		12-44	
12-45		12-46	
12-47		12-48	
12-49		12-50	
12-51		12-52	
12-53		12-54	
12-55		12-56	
12-57		12-58	
12-59		12-60	
12-61		12-62	
12-63		12-64	
12-65		12-66	
12-67		12-68	
12-69		12-70	
12-71		12-72	

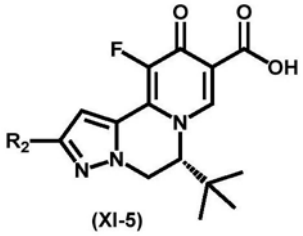
[0284]

12-73		12-74	
12-75		12-76	
12-77		12-78	
12-79		12-80	
12-81		12-82	
12-83		12-84	
12-85		12-86	
12-87		12-88	
12-89		12-90	
12-91		12-92	
12-93		12-94	
12-95		12-96	
12-97		12-98	

[0285]

12-99		12-100	
12-101		12-102	
12-103		12-104	
12-105		12-106	
12-107		12-108	
12-109		12-110	

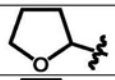
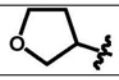
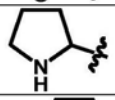
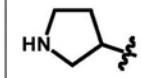
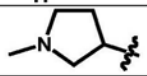
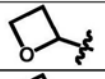
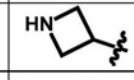
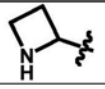
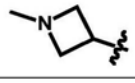
[0286] 本发明的代表性化合物包括但不限于根据式(XI-5)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表13中定义。

[0287] 

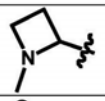
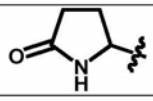
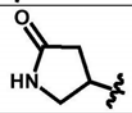
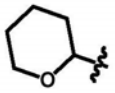
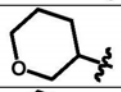
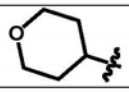
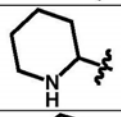
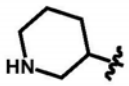
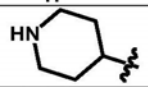
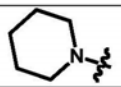
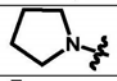
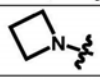
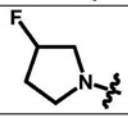
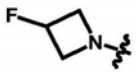
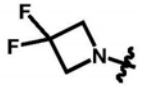
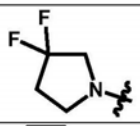
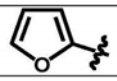
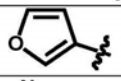
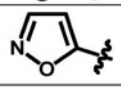
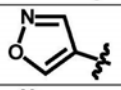
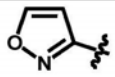
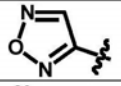
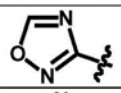
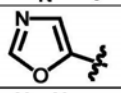
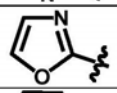
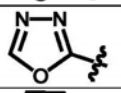
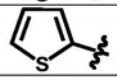
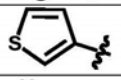
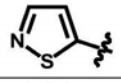
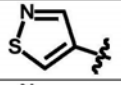
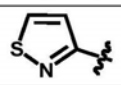
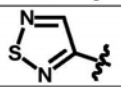
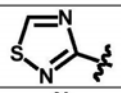
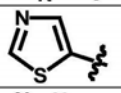
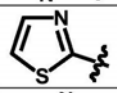
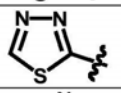
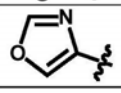
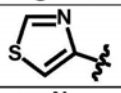
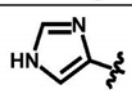
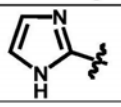
(XI-5)

[0288] 表13

[0289]

化合物	R_2	化合物	R_2
13-1		13-2	
13-3		13-4	
13-5		13-6	
13-7		13-8	
13-9		13-10	

[0290]

13-11		13-12	
13-13		13-14	
13-15		13-16	
13-17		13-18	
13-19		13-20	
13-21		13-22	
13-23		13-24	
13-25		13-26	
13-27		13-28	
13-29		13-30	
13-31		13-32	
13-33		13-34	
13-35		13-36	
13-37		13-38	
13-39		13-40	
13-41		13-42	
13-43		13-44	
13-45		13-46	
13-47		13-48	
13-49		13-50	

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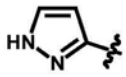
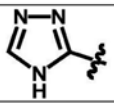
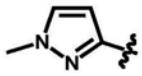
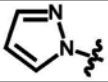
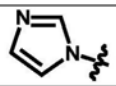
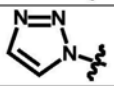
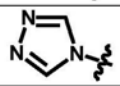
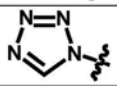
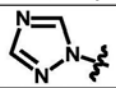
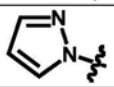
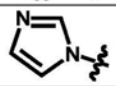
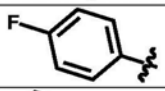
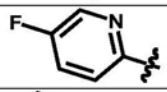
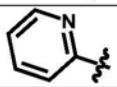
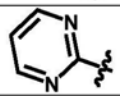
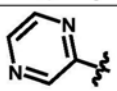
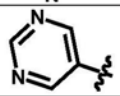
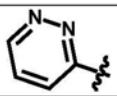
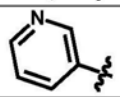
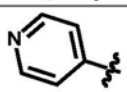
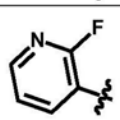
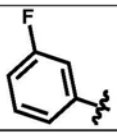
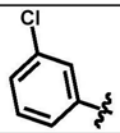
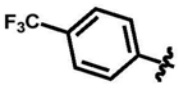
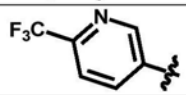
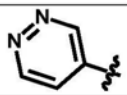
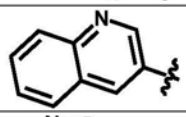
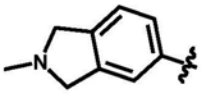
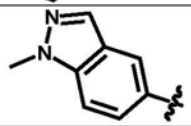
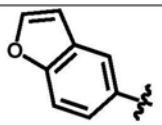
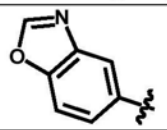
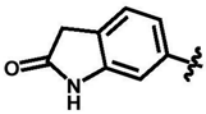
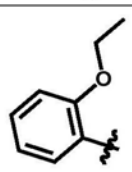
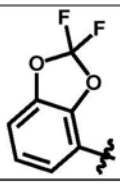
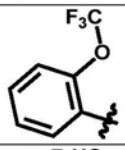
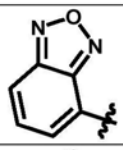
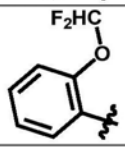
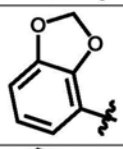
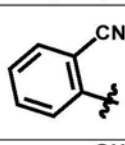
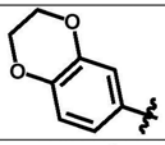
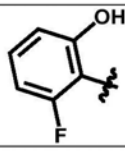
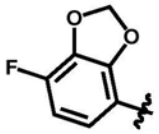
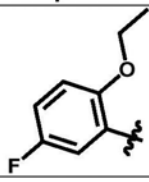
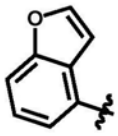
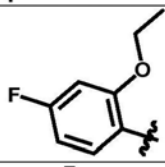
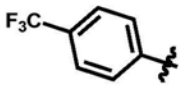
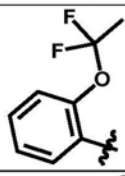
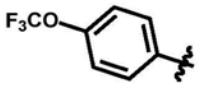
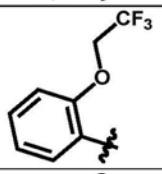
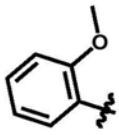
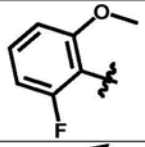
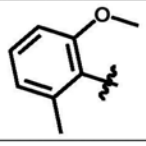
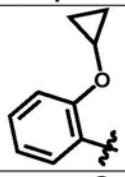
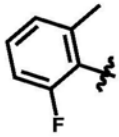
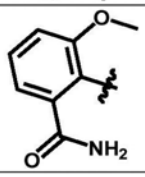
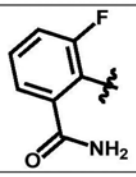
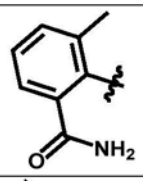
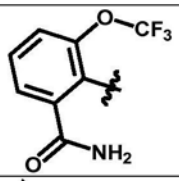
13-51		13-52	
13-53		13-54	
13-55		13-56	
13-57		13-58	
13-59		13-60	
13-61		13-62	
13-63		13-64	
13-65		13-66	
13-67		13-68	
13-69		13-70	
13-71		13-72	
13-73		13-74	
13-75		13-76	
13-77		13-78	
13-79		13-80	
13-81		13-82	
13-83		13-84	

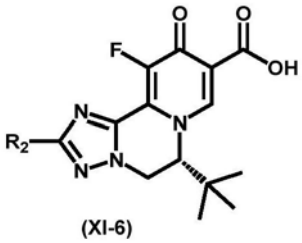
[0292]

13-85		13-86	
13-87		13-88	
13-89		13-90	
13-91		13-92	
13-93		13-94	
13-95		13-96	
13-97		13-98	
13-99		13-100	
13-101		13-102	
13-103		13-104	
13-105		13-106	

[0293]

13-107		13-108	
13-109		13-110	

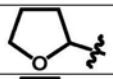
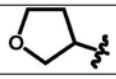
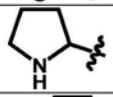
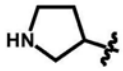
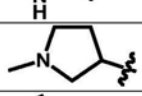
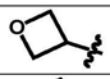
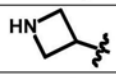
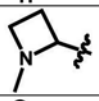
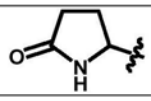
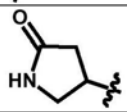
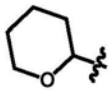
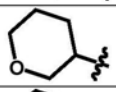
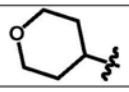
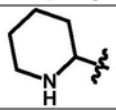
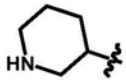
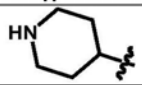
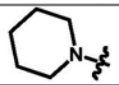
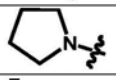
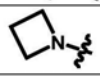
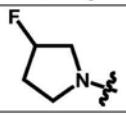
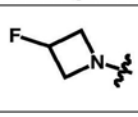
[0294] 本发明的代表性化合物包括但不限于根据式(XI-6)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表14中定义。

[0295] 

(XI-6)

[0296] 表14

[0297]

化合物	R_2	化合物	R_2
14-1		14-2	
14-3		14-4	
14-5		14-6	
14-7		14-8	
14-9		14-10	
14-11		14-12	
14-13		14-14	
14-15		14-16	
14-17		14-18	
14-19		14-20	
14-21		14-22	
14-23		14-24	

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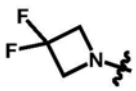
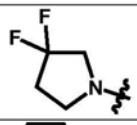
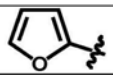
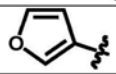
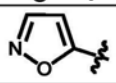
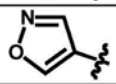
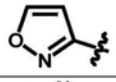
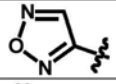
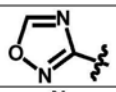
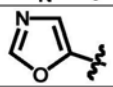
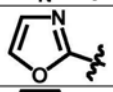
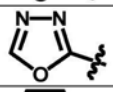
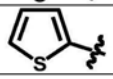
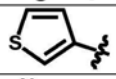
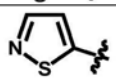
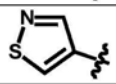
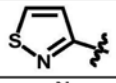
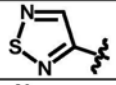
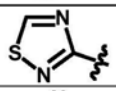
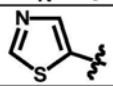
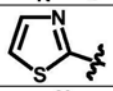
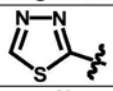
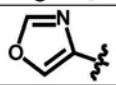
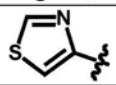
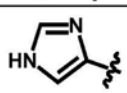
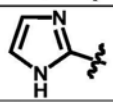
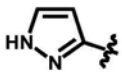
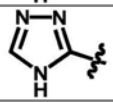
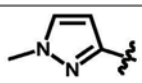
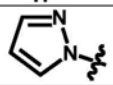
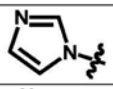
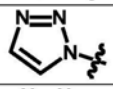
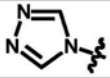
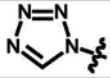
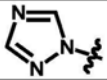
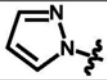
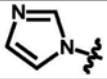
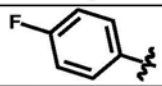
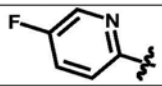
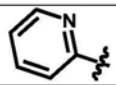
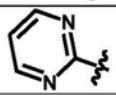
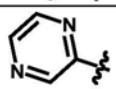
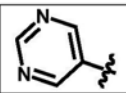
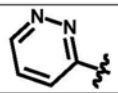
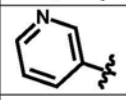
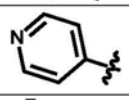
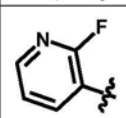
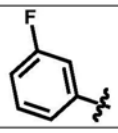
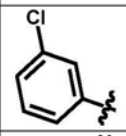
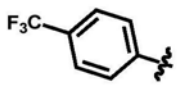
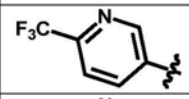
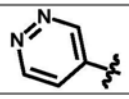
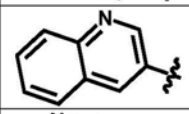
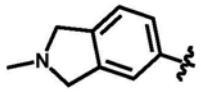
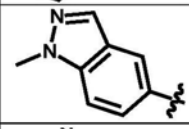
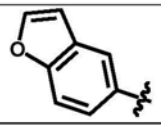
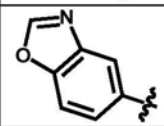
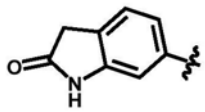
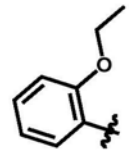
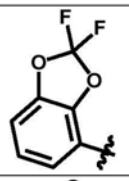
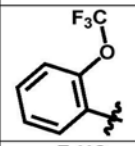
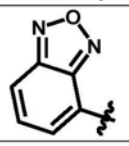
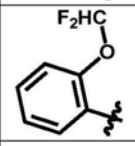
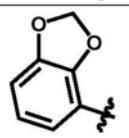
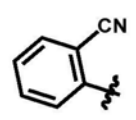
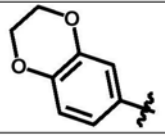
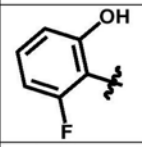
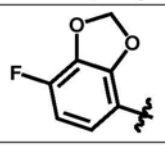
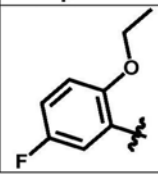
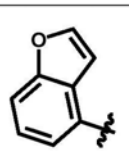
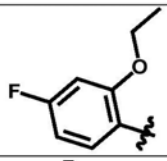
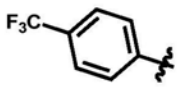
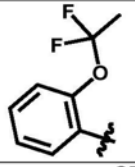
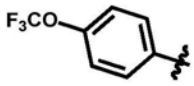
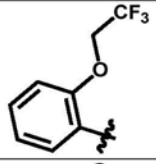
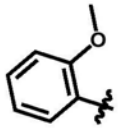
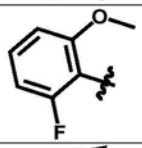
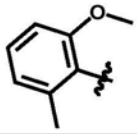
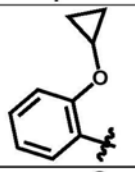
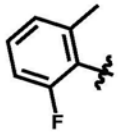
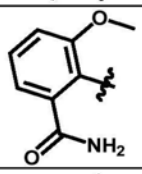
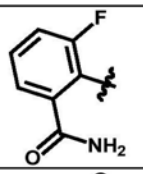
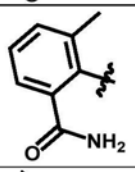
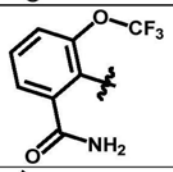
14-25		14-26	
14-27		14-28	
14-29		14-30	
14-31		14-32	
14-33		14-34	
14-35		14-36	
14-37		14-38	
14-39		14-40	
14-41		14-42	
14-43		14-44	
14-45		14-46	
14-47		14-48	
14-49		14-50	
14-51		14-52	
14-53		14-54	
14-55		14-56	
14-57		14-58	
14-59		14-60	
14-61		14-62	
14-63		14-64	
14-65		14-66	

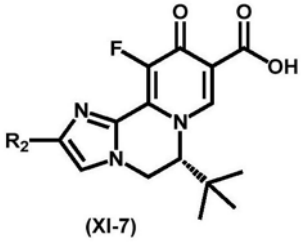
[0299]

14-67		14-68	
14-69		14-70	
14-71		14-72	
14-73		14-74	
14-75		14-76	
14-77		14-78	
14-79		14-80	
14-81		14-82	
14-83		14-84	
14-85		14-86	
14-87		14-88	
14-89		14-90	
14-91		14-92	
14-93		14-94	

[0300]

14-95		14-96	
14-97		14-98	
14-99		14-100	
14-101		14-102	
14-103		14-104	
14-105		14-106	
14-107		14-108	
14-109		14-110	

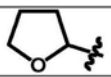
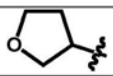
[0301] 本发明的代表性化合物包括但不限于根据式(XI-7)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表15中定义。

[0302] 

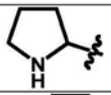
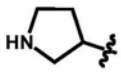
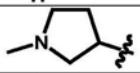
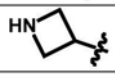
(XI-7)

[0303] 表15

[0304]

化合物	R2	化合物	R2
15-1		15-2	

[0305]

15-3		15-4	
15-5		15-6	
15-7		15-8	
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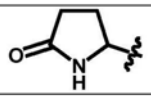
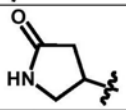
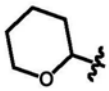
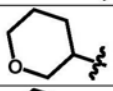
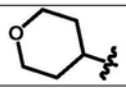
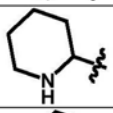
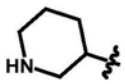
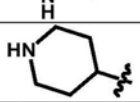
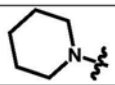
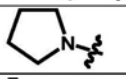
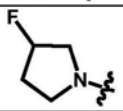
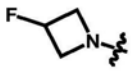
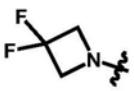
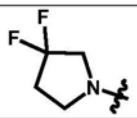
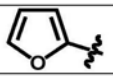
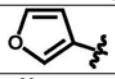
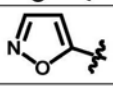
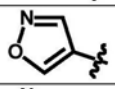
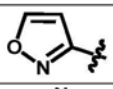
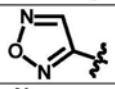
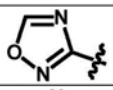
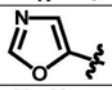
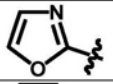
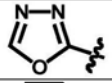
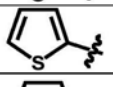
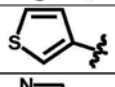
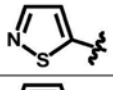
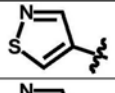
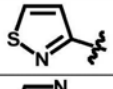
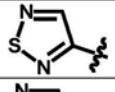
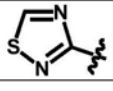
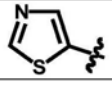
15-11		15-12	
15-13		15-14	
15-15		15-16	
15-17		15-18	
15-19		15-20	
15-21		15-22	
15-23		15-24	
15-25		15-26	
15-27		15-28	
15-29		15-30	
15-31		15-32	
15-33		15-34	
15-35		15-36	
15-37		15-38	
15-39		15-40	
15-41		15-42	
15-43		15-44	

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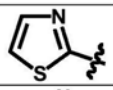
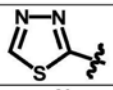
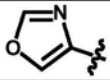
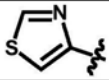
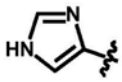
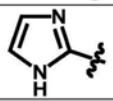
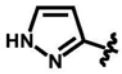
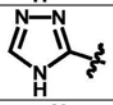
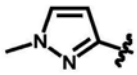
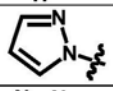
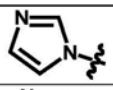
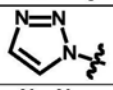
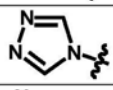
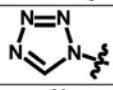
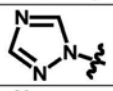
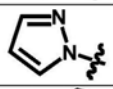
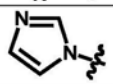
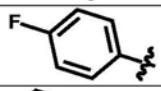
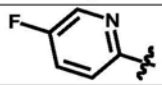
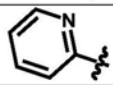
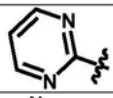
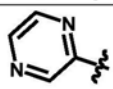
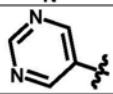
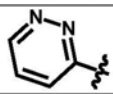
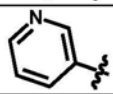
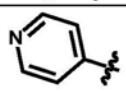
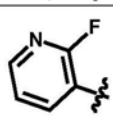
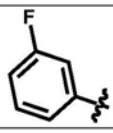
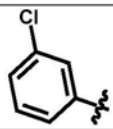
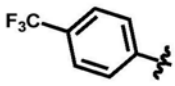
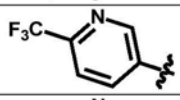
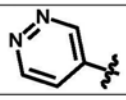
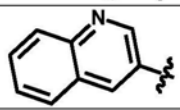
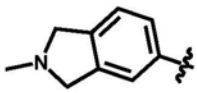
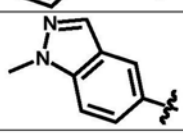
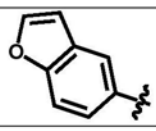
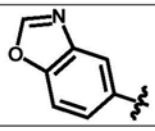
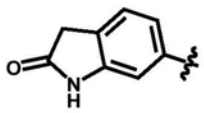
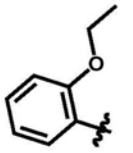
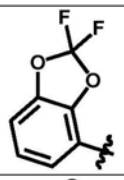
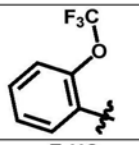
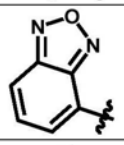
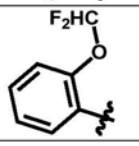
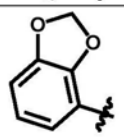
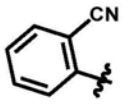
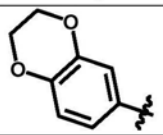
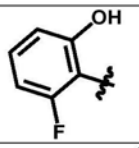
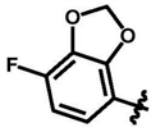
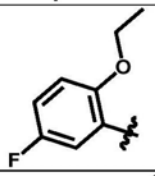
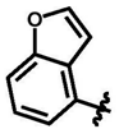
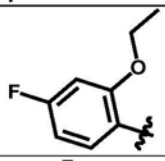
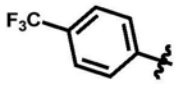
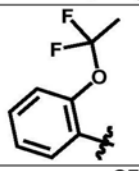
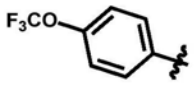
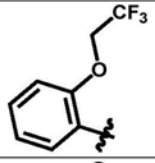
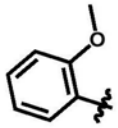
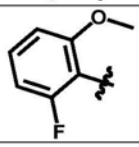
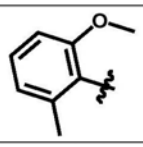
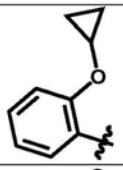
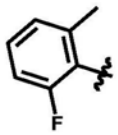
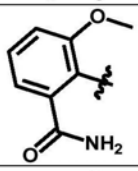
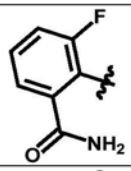
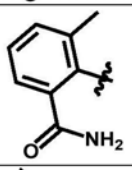
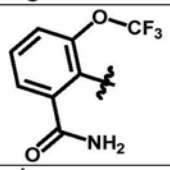
15-45		15-46	
15-47		15-48	
15-49		15-50	
15-51		15-52	
15-53		15-54	
15-55		15-56	
15-57		15-58	
15-59		15-60	
15-61		15-62	
15-63		15-64	
15-65		15-66	
15-67		15-68	
15-69		15-70	
15-71		15-72	
15-73		15-74	
15-75		15-76	
15-77		15-78	
15-79		15-80	

[0307]

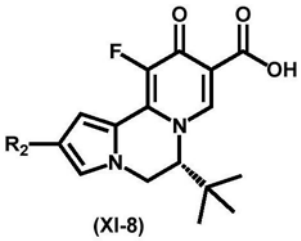
15-81		15-82	
15-83		15-84	
15-85		15-86	
15-87		15-88	
15-89		15-90	
15-91		15-92	
15-93		15-94	
15-95		15-96	
15-97		15-98	
15-99		15-100	
15-101		15-102	

[0308]

15-103		15-104	
15-105		15-106	
15-107		15-108	
15-109		15-110	

[0309] 本发明的代表性化合物包括但不限于根据式(XI-8)的化合物,及其药学上可接受的盐,其中每一种化合物的R_2在表16中定义。

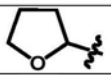
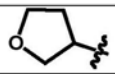
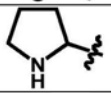
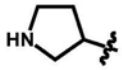
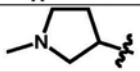
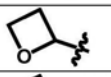
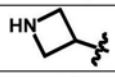
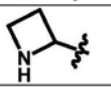
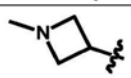
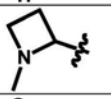
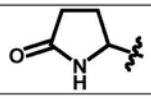
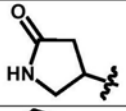
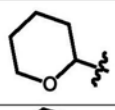
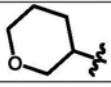
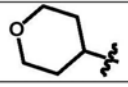
[0310]



(XI-8)

[0311] 表16

[0312]

化合物	R_2	化合物	R_2
16-1		16-2	
16-3		16-4	
16-5		16-6	
16-7		16-8	
16-9		16-10	
16-11		16-12	
16-13		16-14	
16-15		16-16	

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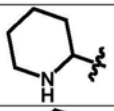
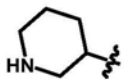
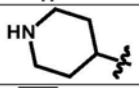
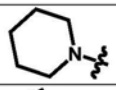
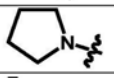
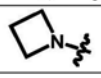
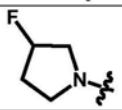
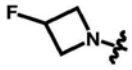
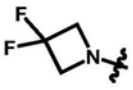
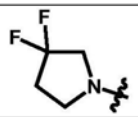
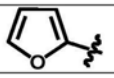
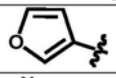
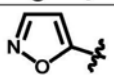
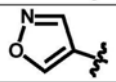
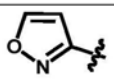
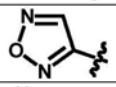
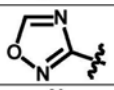
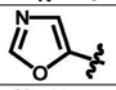
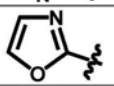
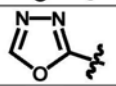
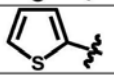
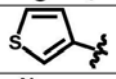
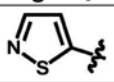
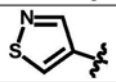
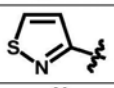
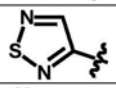
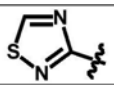
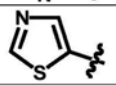
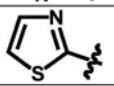
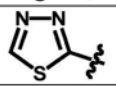
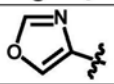
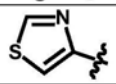
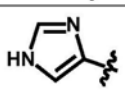
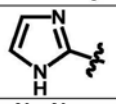
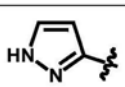
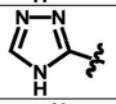
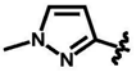
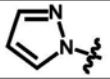
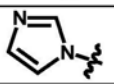
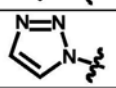
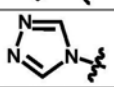
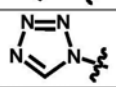
16-17		16-18	
16-19		16-20	
16-21		16-22	
16-23		16-24	
16-25		16-26	
16-27		16-28	
16-29		16-30	
16-31		16-32	
16-33		16-34	
16-35		16-36	
16-37		16-38	
16-39		16-40	
16-41		16-42	
16-43		16-44	
16-45		16-46	
16-47		16-48	
16-49		16-50	
16-51		16-52	
16-53		16-54	
16-55		16-56	
16-57		16-58	

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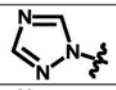
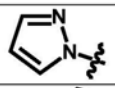
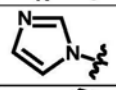
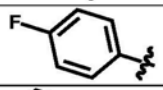
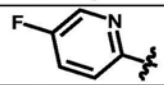
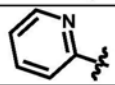
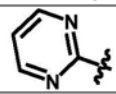
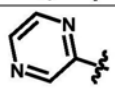
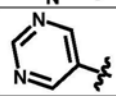
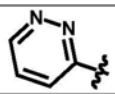
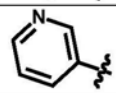
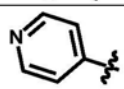
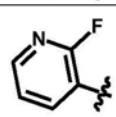
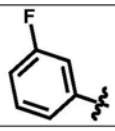
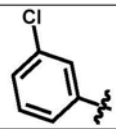
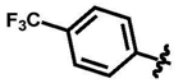
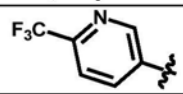
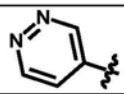
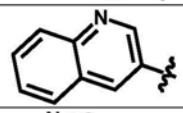
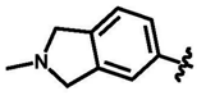
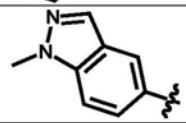
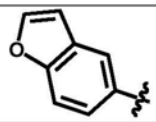
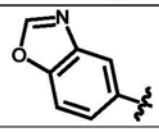
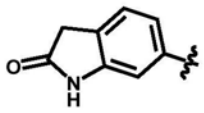
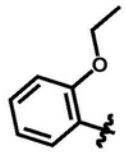
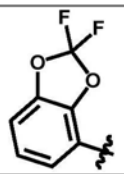
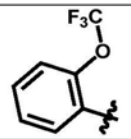
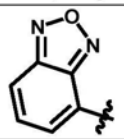
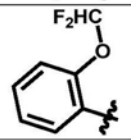
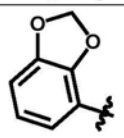
16-59		16-60	
16-61		16-62	
16-63		16-64	
16-65		16-66	
16-67		16-68	
16-69		16-70	
16-71		16-72	
16-73		16-74	
16-75		16-76	
16-77		16-78	
16-79		16-80	
16-81		16-82	
16-83		16-84	
16-85		16-86	
16-87		16-88	

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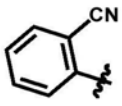
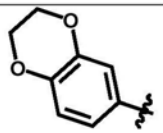
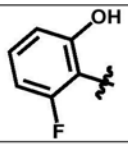
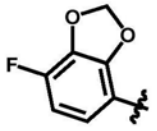
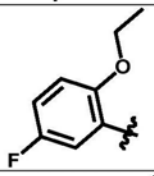
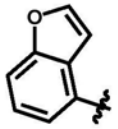
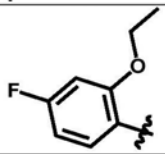
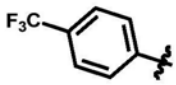
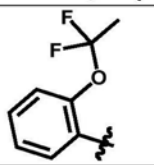
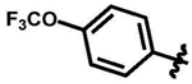
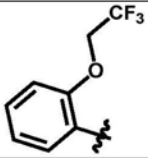
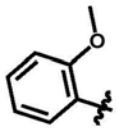
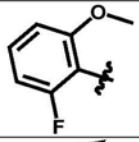
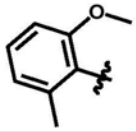
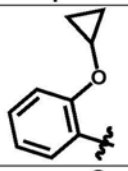
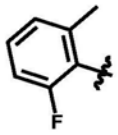
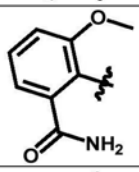
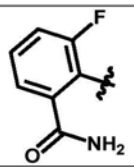
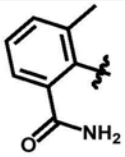
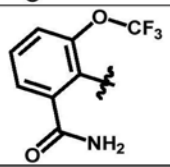
16-89		16-90	
16-91		16-92	
16-93		16-94	
16-95		16-96	
16-97		16-98	
16-99		16-100	
16-101		16-102	
16-103		16-104	
16-105		16-106	
16-107		16-108	
16-109		16-110	

[0316] 应当理解，本文对本发明的描述应当被解释为与化学键合的定律和原理一致。在一些情况下，为了在任何给定的位置容纳取代基，可能需要去除氢原子。

[0317] 还应当理解，本发明的化合物可以包含一个或多个不对称碳原子，并且可以外消旋、非对映异构体和光学活性形式存在。仍然应当理解，本发明的某些化合物可以以不同的互变异构形式存在。所有互变异构体都被认为在本发明的范围内。

[0318] 在一种实施方式中，本文所述的化合物适用于单一疗法，并且对天然或原生HBV株和对目前已知药物具有抗性的HBV株有效。在另一种实施方式中，本文所述的化合物适用于联合疗法。

[0319] 在另一种实施方式中，本发明的化合物可用于调节(例如，抑制、破坏或加速)HBV cccDNA活性的方法中。在又另一种实施方式中，本发明的化合物可用于减少或预防HBV cccDNA形成的方法中。在另一种实施方式中，附加的治疗剂选自核心抑制剂，其包括GLS4、GLS4JHS、JNJ-379、ABI-H0731、ABI-H2158、AB-423、AB-506、WX-066和QL-0A6A；免疫调节剂或免疫刺激剂疗法，其包括T细胞应答激活剂AIC649和属于干扰素类的生物剂，诸如干扰素α2a或2b或修饰的干扰素，诸如聚乙二醇化干扰素、α2a、α2b、λ；或STING(干扰素基因的刺激剂)调节剂；或TLR调节剂诸如TLR-7激动剂、TLR-8激动剂或TLR-9激动剂；或者用来刺激HBV特异性免疫应答的治疗性疫苗，诸如由HBcAg和HBsAg组成的病毒样颗粒，HBsAg和HBsAb的免疫复合物，或在酵母载体环境中包括HBx、HBsAg和HBcAg的重组蛋白；或某些细胞病毒RNA传感器诸如RIG-I、NOD2和MDA5蛋白的免疫激活剂诸如SB-9200；或RNA干扰(RNAi)或小干扰RNA(siRNA)诸如ARC-520、ARC-521、ARB-1467和ALN-HBV RNAi；或阻止病毒进入或成熟或靶向HBV聚合酶的抗病毒剂，诸如核苷或核苷酸或非核苷(或非核苷酸)聚合酶抑制剂，以及具有不同或未知机制的剂，包括破坏HBV复制或持久性所需的一种或多种其他必需病毒蛋白或宿主蛋白功能的剂，诸如REP 2139、RG7834和AB-452。在联合疗法的实施方式中，逆转录酶抑制剂是齐多夫定(Zidovudine)、去羟肌苷(Didanosine)、扎西他滨(Zalcitabine)、ddA、司他夫定(Stavudine)、拉米夫定(Lamivudine)、阿巴卡韦(Abacavir)、恩曲他滨(Emtricitabine)、恩替卡韦、阿立他滨(Apricitabine)、阿替韦拉平(Atevirapine)、利巴韦林(ribavirin)、阿昔洛韦(acyclovir)、泛昔洛韦(famciclovir)、伐昔洛韦(valacyclovir)、更昔洛韦(ganciclovir)、缬更昔洛韦(valganciclovir)、替诺福韦、阿德福韦(Adefovir)、PMPA、西多福韦(cidofovir)、依法韦仑(Efavirenz)、奈韦拉平(Nevirapine)、地拉韦啶(Delavirdine)或依曲韦林(Etravirine)中的至少一种。

[0320] 在联合疗法的另一种实施方式中，TLR-7激动剂选自由以下组成的组：SM360320(12-苄基-8-羟基-2-(2-甲氧基-乙氧基)腺嘌呤)、AZD8848([3-({[3-(6-氨基-2-丁氧基-8-氧亚基-7,8-二氢-9H-嘌呤-12-基)丙基][3-(4-吗啉基)丙基]氨基}甲基)苯基]乙酸甲酯)、GS-9620(4-氨基-2-丁氧基-8-[3-(2-吡咯烷基甲基)苄基]-7,8-二氢-6(5H)-蝶啶酮)、AL-034(TQ-A3334)和RO6864018。

[0321] 在联合疗法的另一种实施方式中，TLR-8激动剂是GS-9688。

[0322] 在这些联合疗法的实施方式中，化合物和附加的治疗剂共同配制。在另一种实施方式中，共同给药化合物和附加的治疗剂。

[0323] 在联合疗法的另一种实施方式中，与单独给药至少一种附加的治疗剂相比，给药本发明的化合物允许以实现预防性地治疗有此需要的个体的HBV感染的类似结果所需的较低剂量或频率给药附加的治疗剂。

[0324] 在联合疗法的另一种实施方式中，在给药治疗有效量的本发明的化合物之前，已知该个体对选自由HBV聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同的衣壳组装调节剂、不同或未知机制的抗病毒化合物及其组合组成的组的化合物是难治的。

[0325] 在该方法的还另一种实施方式中，与给药选自由以下组成的组的化合物相比：HBV

聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同的衣壳组装调节剂、不同或未知机制的抗病毒化合物及其组合，给药本发明的化合物在更大程度上降低个体的病毒载量。

[0326] 在另一种实施方式中，给药本发明的化合物导致病毒突变和/或病毒抗性的发生率低于给药选自由HBV聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同的衣壳组装调节剂、不同或未知机制的抗病毒化合物及其组合组成的组的化合物。

[0327] 应当理解，由本发明包括的化合物是适当地稳定以用作药剂的那些。

[0328] 定义

[0329] 下面列出的是用于描述本发明的各种术语的定义。这些定义适用于如在整个说明书和权利要求中使用的术语，除非在具体情况下另有限制，无论是单独还是作为较大组的一部分。

[0330] 如本文所用，术语“芳基”是指包括至少一个芳环的单环或多环碳环体系，包括但不限于苯基、萘基、四氢萘基、茚满基和茚基。多环芳基是包括至少一个芳环的多环体系。多环芳基可包括稠环、共价连接的环或其组合。

[0331] 如本文所用，术语“杂芳基”是指具有选自S、O和N的一个或多个环原子的单环或多环芳族基团；并且其余的环原子是碳，其中环中包含的任何N或S都可以被任选地氧化。杂芳基包括但不限于吡啶基、吡嗪基、嘧啶基、吡咯基、吡唑基、咪唑基、噻唑基、噁唑基、异噁唑基、噻二唑基、噁二唑基、噻吩基、呋喃基、喹啉基、异喹啉基、苯并咪唑基、苯并噁唑基、喹喔啉基。多环杂芳基可包括稠环、共价连接的环或其组合。

[0332] 根据本发明，芳族基团可以是取代的或未取代的。

[0333] 如本文所用，术语“烷基”是指饱和的、直链或支链的烃基团。“$C_{2-}C_4$烷基”、“$C_{2-}C_6$烷基”、“$C_{2-}C_8$烷基”、“$C_{2-}C_{12}$烷基”、“C_2-C_4烷基”或“C_3-C_6烷基”是指分别包含一至四、一至六、一至八、一至十二、2至4和3至6个碳原子的烷基基团。C_2-C_8烷基基团的实例包括但不限于甲基、乙基、丙基、异丙基、正丁基、叔丁基、新戊基、正己基、庚基和辛基基团。

[0334] 如本文所用，术语“烯基”是指通过去除单个氢原子而具有至少一个碳-碳双键的直链或支链烃基团。“C_2-C_8烯基”、“C_2-C_{12}烯基”、“C_2-C_4烯基”、“C_3-C_4烯基”或“C_3-C_6烯基”是指分别包含二至八、二至十二、二至四、三至四或三至六个碳原子的烯基基团。烯基基团包括但不限于例如乙烯基、丙烯基、丁烯基、2-甲基-2-丁烯-2-基、庚烯基、辛烯基等。

[0335] 如本文所用，术语“炔基”是指通过去除单个氢原子而具有至少一个碳-碳双键的直链或支链烃基团。“C_2-C_8炔基”、“C_2-C_{12}炔基”、“C_2-C_4炔基”、“C_3-C_4炔基”或“C_3-C_6炔基”是指分别包含二至八、二至十二、二至四、三至四或三至六个碳原子的炔基基团。代表性的炔基基团包括但不限于例如乙炔基、2-丙炔基、2-丁炔基、庚炔基、辛炔基等。

[0336] 如本文所用，术语“环烷基”是指单环或多环饱和碳环或者双或三环基团稠合、桥连或螺的体系，并且碳原子可以任选地被氧亚基取代或任选地被环外烯属双键取代。优选的环烷基基团包括C_3-C_{12}环烷基、C_3-C_6环烷基、C_3-C_8环烷基以及C_4-C_7环烷基。C_3-C_{12}环烷基的实例包括但不限于环丙基、环丁基、环戊基、环己基、环戊基、环辛基、4-亚甲基-环己基、双环[2.2.1]庚基、双环[3.1.0]己基、螺[2.5]辛基、3-亚甲基双环[3.2.1]辛基、螺[4.4]壬基等。

[0337] 如本文所用，术语“环烯基”是指具有至少一个碳-碳双键的单环或多环碳环或者

双或三环基团稠合、桥连或螺的体系，并且碳原子可以任选地被氧亚基取代或任选地被环外烯属双键取代。优选的环烯基基团包括C_3-C_{12}环烯基、C_3-C_8环烯基或C_5-C_7环烯基基团。C_3-C_{12}环烯基的实例包括但不限于环丙烯基、环丁烯基、环戊烯基、环己烯基、环庚烯基、环辛烯基、双环[2.2.1]庚-2-烯基、双环[3.1.0]己-2-烯基、螺[2.5]辛-4-烯基、螺[4.4]壬-2-烯基、双环[4.2.1]壬-3-烯-12-基等。

[0338] 如本文所用，术语“芳基烷基”是指其中亚烷基链连接至芳基基团的官能团，例如-CH_2CH_2-苯基。术语“取代的芳基烷基”是指其中芳基基团被取代的芳基烷基官能团。类似地，术语“杂芳基烷基”是指其中亚烷基链连接至杂芳基基团的官能团。术语“取代的杂芳基烷基”是指其中杂芳基基团被取代的杂芳基烷基官能团。

[0339] 如本文所用，除非另有说明，否则单独或与其他术语组合使用的术语“烷氧基”意指具有指定数目的碳原子的烷基基团经由氧原子连接至分子的其余部分，诸如例如，甲氧基、乙氧基、2-丙氧基、2-丙氧基(异丙氧基)以及更高级同系物和异构体。优选的烷氧基是(C_2-C_3)烷氧基。

[0340] 应当理解，本文所述的任何烷基、烯基、炔基、环烷基、杂环和环烯基部分也可以是脂族基团或脂环族基团。

[0341] “脂族”基团是由碳原子、氢原子、卤素原子、氧、氮或其他原子的任何组合组成的非芳族部分，并且任选地包含一个或多个不饱和单元，例如，双键和/或三键。脂族基团的实例是官能团，诸如烷基、烯基、炔基、O、OH、NH、NH_2、C(O)、S(O)$_2$、C(O)O、C(O)NH、OC(O)O、OC(O)NH、OC(O)NH_2、S(O)$_2$NH、S(O)$_2$$NH_2$、NHC(O)$NH_2$、NHC(O)C(O)NH、NHS(O)$_2$NH、NHS(O)$_2$$NH_2$、C(O)NHS(O)$_2$、C(O)NHS(O)$_2$NH或C(O)NHS(O)$_2$$NH_2$等，包括一个或多个官能团、非芳族烃(任选取代的)的基团，以及其中非芳族烃(任选取代的)的一个或多个碳被官能团替代的基团。脂族基团的碳原子可以任选地被氧亚基取代。脂族基团可以是直链、支链、环状或其组合，并且优选地包含约1至约24个碳原子，更通常约1至约12个碳原子。除如本文所用的脂族烃基团外，脂族基团明确地还包括例如烷氧基烷基、多烷氧基烷基，诸如例如聚亚烷基二醇、聚胺和聚亚胺。脂族基团可以被任选地取代。

[0342] 术语“杂环”或“杂环烷基”可以互换使用，并且是指非芳环或者双或三环基团稠合、桥连或螺的体系，其中(i)每个环体系包含独立地选自氧、硫和氮的至少一个杂原子，(ii)每个环体系可以是饱和或不饱和的，(iii)氮和硫杂原子可任选被氧化，(iv)氮杂原子可任选被季铵化，(v)上述任一种环可以稠合到芳环上，以及(vi)其余的环原子是碳原子，其可以任选地被氧亚基取代或任选地被环外烯属双键取代。代表性杂环烷基基团包括但不限于1,3-二氧戊环、吡咯烷基、吡唑啉基、吡唑烷基、咪唑啉基、咪唑烷基、哌啶基、哌嗪基、噁唑烷基、异噁唑烷基、吗啉基、四氢噻唑基、异四氢噻唑基、喹喔啉基、哒嗪酮基、2-氮杂双环[2.2.1]-庚基、8-氮杂双环[3.2.1]辛基、5-氮杂螺[2.5]辛基、2-氧杂-7-氮杂螺[4.4]壬基、7-氧亚基氧杂环庚烷-4-基和四氢呋喃基。这样的杂环基团可以被进一步取代。杂芳基或杂环基团可以是C-连接或N-连接的(在可能情况下)。

[0343] 应当理解，本文所述的任何烷基、烯基、炔基、脂环族、环烷基、环烯基、芳基、杂芳基、杂环、脂族部分等，当用作连接两个或更多个基团或取代基(其可以在一个或多个相同或不同的原子上)的连接时，也可以是二价或多价基团。本领域技术人员可以容易地根据其存在的环境中确定任何这样的基团的化合价。

[0344] 术语“取代的”是指通过用取代基独立替代氢原子中的一个、两个或三个或更多个来取代，取代基包括但不限于-F、-Cl、-Br、-I、-OH、C_2-C_{12}-烷基；C_2-C_{12}-烯基、C_2-C_{12}-炔基、-C_3-C_{12}-环烷基、被保护的羟基、-NO_2、-N_3、-CN、-NH_2、被保护的氨基、氧亚基、硫代、-NH-C_2-C_{12}-烷基、-NH-C_2-C_8-烯基、-NH-C_2-C_8-炔基、-NH-C_3-C_{12}-环烷基、-NH-芳基、-NH-杂芳基、-NH-杂环烷基、-二烷基氨基、-二芳基氨基、-二杂芳基氨基、-O-C_2-C_{12}-烷基、-O-C_2-C_8-烯基、-O-C_2-C_8-炔基、-O-C_3-C_{12}-环烷基、-O-芳基、-O-杂芳基、-O-杂环烷基、-C(O)-C_2-C_{12}-烷基、-C(O)-C_2-C_8-烯基、-C(O)-C_2-C_8-炔基、-C(O)-C_3-C_{12}-环烷基、-C(O)-芳基、-C(O)-杂芳基、-C(O)-杂环烷基、-$CONH_2$、-CONH-C_2-C_{12}-烷基、-CONH-C_2-C_8-烯基、-CONH-C_2-C_8-炔基、-CONH-C_3-C_{12}-环烷基、-CONH-芳基、-CONH-杂芳基、-CONH-杂环烷基、-OCO_2-C_2-C_{12}-烷基、-OCO_2-C_2-C_8-烯基、-OCO_2-C_2-C_8-炔基、-OCO_2-C_3-C_{12}-环烷基、-OCO_2-芳基、-OCO_2-杂芳基、-OCO_2-杂环烷基、-CO_2-C_2-C_{12}烷基、-CO_2-C_2-C_8烯基、-CO_2-C_2-C_8炔基、CO_2-C_3-C_{12}-环烷基、-CO_2-芳基、CO_2-杂芳基、CO_2-杂环烷基、-$OCONH_2$、-OCONH-C_2-C_{12}-烷基、-OCONH-C_2-C_8-烯基、-OCONH-C_2-C_8-炔基、-OCONH-C_3-C_{12}-环烷基、-OCONH-芳基、-OCONH-杂芳基、-OCONH-杂环-烷基、-NHC(O)H、-NHC(O)-C_2-C_{12}-烷基、-NHC(O)-C_2-C_8-烯基、-NHC(O)-C_2-C_8-炔基、-NHC(O)-C_3-C_{12}-环烷基、-NHC(O)-芳基、-NHC(O)-杂芳基、-NHC(O)-杂环-烷基、-$NHCO_2$-C_2-C_{12}-烷基、-$NHCO_2$-C_2-C_8-烯基、-$NHCO_2$-C_2-C_8-炔基、-$NHCO_2$-C_3-C_{12}-环烷基、-$NHCO_2$-芳基、-$NHCO_2$-杂芳基、-$NHCO_2$-杂环烷基、-NHC(O)NH_2、-NHC(O)NH-C_2-C_{12}-烷基、-NHC(O)NH-C_2-C_8-烯基、-NHC(O)NH-C_2-C_8-炔基、-NHC(O)NH-C_3-C_{12}-环烷基、-NHC(O)NH-芳基、-NHC(O)NH-杂芳基、-NHC(O)NH-杂环烷基、NHC(S)NH_2、-NHC(S)NH-C_2-C_{12}-烷基、-NHC(S)NH-C_2-C_8-烯基、-NHC(S)NH-C_2-C_8-炔基、-NHC(S)NH-C_3-C_{12}-环烷基、-NHC(S)NH-芳基、-NHC(S)NH-杂芳基、-NHC(S)NH-杂环烷基、-NHC(NH)NH_2、-NHC(NH)NH-C_2-C_{12}-烷基、-NHC(NH)NH-C_2-C_8-烯基、-NHC(NH)NH-C_2-C_8-炔基、-NHC(NH)NH-C_3-C_{12}-环烷基、-NHC(NH)NH-芳基、-NHC(NH)NH-杂芳基、-NHC(NH)NH-杂环烷基、-NHC(NH)-C_2-C_{12}-烷基、-NHC(NH)-C_2-C_8-烯基、-NHC(NH)-C_2-C_8-炔基、-NHC(NH)-C_3-C_{12}-环烷基、-NHC(NH)-芳基、-NHC(NH)-杂芳基、-NHC(NH)-杂环烷基、-C(NH)NH-C_2-C_{12}-烷基、-C(NH)NH-C_2-C_8-烯基、-C(NH)NH-C_2-C_8-炔基、-C(NH)NH-C_3-C_{12}-环烷基、-C(NH)NH-芳基、-C(NH)NH-杂芳基、-C(NH)NH-杂环烷基、-S(O)-C_2-C_{12}-烷基、-S(O)-C_2-C_8-烯基、-S(O)-C_2-C_8-炔基、-S(O)-C_3-C_{12}-环烷基、-S(O)-芳基、-S(O)-杂芳基、-S(O)-杂环烷基、-SO_2NH_2、-SO_2NH-C_2-C_{12}-烷基、-SO_2NH-C_2-C_8-烯基、-SO_2NH-C_2-C_8-炔基、-SO_2NH-C_3-C_{12}-环烷基、-SO_2NH-芳基、-SO_2NH-杂芳基、-SO_2NH-杂环烷基、-$NHSO_2$-C_2-C_{12}-烷基、-$NHSO_2$-C_2-C_8-烯基、-$NHSO_2$-C_2-C_8-炔基、-$NHSO_2$-C_3-C_{12}-环烷基、-$NHSO_2$-芳基、-$NHSO_2$-杂芳基、-$NHSO_2$-杂环烷基、-CH_2NH_2、-$CH_2SO_2CH_3$、-芳基、-芳基烷基、-杂芳基、-杂芳基烷基、-杂环烷基、-C_3-C_{12}-环烷基、多烷氧基烷基、多烷氧基、-甲氧基甲氧基、-甲氧基乙氧基、-SH、-S-C_2-C_{12}-烷基、-S-C_2-C_8-烯基、-S-C_2-C_8-炔基、-S-C_3-C_{12}-环烷基、-S-芳基、-S-杂芳基、-S-杂环烷基或甲硫基-甲基。在某些实施方式中，取代基独立地选自卤素，优选Cl和F；C_1-C_4-烷基，优选甲基和乙基；卤代-C_1-C_4-烷基，诸如氟甲基、二氟甲基和三氟甲基；C_2-C_4-烯基；卤代-C_2-C_4-烯基；C_3-C_6-环烷基，诸如环丙基；C_1-C_4-烷氧基，诸如甲氧基和乙氧基；卤代-C_1-C_4-烷氧基，诸如氟甲氧基、二氟甲氧基和三氟甲氧基；-CN；-OH；NH_2；C_1-C_4-烷基氨基；二(C_1-C_4-烷基)氨基；以及NO_2。应当理解，芳基、杂芳基、烷基等可以被进一步取代。在一些情况下，取代的部分中的每个取代基附加地被一个或多个基团任选地取代，每个基团独立地选自C_1-C_4-烷基、-CF_3、-OCH_3、-

OCF_3、-F、-Cl、-Br、-I、-OH、$-NO_2$、-CN和$-NH_2$。优选地，取代的烷基基团被一个或多个卤素原子，更优选地一个或多个氟或氯原子取代。

[0345] 如本文所用，术语“卤代(halo)”或卤素(halogen)”单独或作为另一取代基的一部分是指氟、氯、溴或碘原子。

[0346] 如本文所用，术语“任选(地)取代”意指所提及的基团可以是取代的或未取代的。在一种实施方式中，所提及的基团被零个取代基任选取代，即，所提及的基团是未取代的。在另一种实施方式中，所提及的基团被单独且独立地选自本文所述的基团的一个或多个另外的基团任选取代。

[0347] 术语“氢”包括氢和氘。另外，原子的详述包括该原子的其他同位素，只要所得化合物是药学上可接受的。

[0348] 如本文所用，术语“羟基活化基团”是指本领域已知的活化羟基基团以使其在合成程序中诸如在取代或消除反应中脱离的不稳定化学部分。羟基活化基团的实例包括但不限于甲磺酸酯、甲苯磺酸酯、三氟甲磺酸酯、对硝基苯甲酸酯、膦酸酯等。

[0349] 如本文所用，术语“活化的羟基”是指被如上定义的羟基活化基团活化的羟基基团，包括例如甲磺酸酯、甲苯磺酸酯、三氟甲磺酸酯、对硝基苯甲酸酯、膦酸酯基团。

[0350] 如本文所用，术语“羟基保护基团”是指在本领域中已知用于保护羟基基团免于在合成程序期间发生不希望的反应的不稳定化学部分。在一个或多个所述合成程序之后，可以选择性地去除如本文所述的羟基保护基团。在T.H.Greene and P.G.M.Wuts,Protective Groups in Organic Synthesis,3rd edition,John Wiley&Sons,New York(1999)中总体上描述了如本领域已知的羟基保护基团。羟基保护基团的实例包括苄氧基羰基、4-甲氧基苄氧基羰基、叔丁氧基-羰基、异丙氧基羰基、二苯基甲氧基羰基、2,2,2-三氯乙氧基羰基、烯丙氧基羰基、乙酰基、甲酰基、氯乙酰基、三氟乙酰基、甲氧基乙酰基、苯氧基乙酰基、苯甲酰基、甲基、叔丁基、2,2,2-三氯乙基、2-三甲基硅烷基乙基、烯丙基、苄基、三苯基-甲基(三苯甲基)、甲氧基甲基、甲硫基甲基、苄氧基甲基、2-(三甲基硅烷基)-乙氧基甲基、甲磺酰基、三甲基硅烷基、三异丙基硅烷基等。

[0351] 如本文所用，术语“被保护的羟基”是指被如上所定义的羟基保护基团保护的羟基基团，包括例如苯甲酰基、乙酰基、三甲基硅烷基、三乙基硅烷基、甲氧基甲基基团。

[0352] 如本文所用，术语“羟基前药基团”是指在本领域中已知的通过覆盖或掩蔽羟基基团以瞬时方式改变母体药物的物理化学特性并从而改变生物特性的前部分(promoiety)基团。在一个或多个所述合成程序之后，如本文所述的羟基前药基团必须能够在体内恢复回到羟基基团。在Kenneth B.Sloan,Prodrugs,Topical and Ocular Drug Delivery,(Drugs and the Pharmaceutical Sciences;Volume 53),Marcel Dekker,Inc.,New York(1992)中总体上描述了如本领域已知的羟基前药基团。

[0353] 如本文所用，术语“氨基保护基团”是指在本领域中已知用于保护氨基基团免于在合成程序期间发生不希望的反应的不稳定化学部分。在一个或多个所述合成程序之后，可以选择性地去除如本文所述的氨基保护基团。在T.H.Greene and P.G.M.Wuts,Protective Groups in Organic Synthesis,3rd edition,John Wiley&Sons,New York(1999)中总体上描述了如本领域已知的氨基保护基团。氨基保护基团的实例包括但不限于甲氧基羰基、叔丁氧基羰基、12-芴基-甲氧基羰基、苄氧基羰基等。

[0354] 如本文所用,术语“被保护的氨基”是指用如上定义的氨基保护基团保护的氨基基团。

[0355] 术语“离去基团”意指可以在取代反应诸如亲核取代反应中被其他官能团或原子置换的官能团或原子。举例来说,代表性离去基团包括氯、溴和碘基团;磺酸酯基团,诸如甲磺酸酯、甲苯磺酸酯、对溴苯磺酸酯、间硝基苯磺酸酯(nosylate)等;以及酰氧基基团,诸如乙酰氧基、三氟乙酰氧基等。

[0356] 如本文所用,术语“非质子溶剂”是指对质子活性相对惰性的溶剂,即不充当质子给体。实例包括但不限于烃,诸如己烷和甲苯,例如卤代烃,诸如例如二氯甲烷、二氯乙烷、氯仿等,杂环化合物,诸如例如四氢呋喃和N-甲基吡咯烷酮,以及醚,诸如二乙醚、双甲氧基甲基醚。这样的化合物是本领域技术人员众所周知的,并且对于本领域技术人员将显而易见的是,对于特定的化合物和反应条件,个别的溶剂或其混合物可能是优选的,这取决于这样的因素,例如试剂的溶解度、试剂的反应性和优选的温度范围。非质子溶剂的进一步讨论可以在有机化学教科书或专业专题著作中找到,例如:Organic Solvents Physical Properties and Methods of Purification,4th ed.,edited by John A.Riddick et al.,Vol.II,in the Techniques of Chemistry Series,John Wiley&Sons,NY,1986。

[0357] 如本文所用,术语“质子溶剂”是指倾向于提供质子的溶剂,诸如醇,例如甲醇、乙醇、丙醇、异丙醇、丁醇、叔丁醇等。这样的溶剂是本领域技术人员众所周知的,并且对于本领域技术人员将显而易见的是,对于特定的化合物和反应条件,个别的溶剂或其混合物可能是优选的,这取决于这样的因素,例如试剂的溶解度、试剂的反应性和优选的温度范围。给质子溶剂的进一步讨论可以在有机化学教科书或专业专题著作中找到,例如:Organic Solvents Physical Properties and Methods of Purification,4th ed.,edited by John A.Riddick et al.,Vol.II,in the Techniques of Chemistry Series,John Wiley&Sons,NY,1986。

[0358] 本发明所设想的取代基和变量的组合仅是导致形成稳定化合物的那些。如本文所用,术语“稳定的”是指化合物具有足以允许制备的稳定性,并且化合物的完整性保持足够长的时间以可用于本文详述的目的(例如,治疗性或预防性给药至受试者)。

[0359] 合成的化合物可以从反应混合物中分离出来,并通过诸如柱色谱、高压液相色谱或重结晶的方法进一步纯化。如技术人员可以理解的,合成本文式的化合物的另外方法对于本领域普通技术人员来说将是显而易见的。另外,各种合成步骤可以以交替的序列或顺序进行以得到所需的化合物。可用于合成本文所述的化合物的合成化学转化和保护基团方法(保护和去保护)是本领域已知的并且包括,例如,诸如在以下中描述的那些:R.Larock,Comprehensive Organic Transformations,2nd Ed.Wiley-VCH(1999);T.W.Greene and P.G.M.Wuts,Protective Groups in Organic Synthesis,3rd Ed.,John Wiley and Sons(1999);L.Fieser and M.Fieser,Fieser and Fieser's Reagents for Organic Synthesis,John Wiley and Sons(1994);以及L.Paquette,ed.,Encyclopedia of Reagents for Organic Synthesis,John Wiley and Sons(1995),及其后续版本。

[0360] 如本文所用,术语“受试者”是指动物。优选地,动物是哺乳动物。更优选地,哺乳动物是人。受试者还是指例如狗、猫、马、牛、猪、豚鼠、鱼、鸟等。

[0361] 可以通过附加适当的官能度来改性本发明的化合物,以增强选择性生物特性。这

样的改性在本领域是已知的并且可以包括增加到给定生物系统(例如,血液、淋巴系统、中枢神经系统)的生物渗透、增加口服利用度、增加溶解度以允许通过注射给药、改变代谢和改变排泄率的那些。

[0362] 本文所述的化合物包含一个或多个不对称中心,并因此产生对映异构体、非对映异构体和其他立体异构形式,它们可以按照绝对立体化学定义为(R)-或(S)-,或者对于氨基酸定义为(D)-或(L)-。本发明意指包括所有这些可能的异构体,以及它们的外消旋和光学纯形式。光学异构体可以通过上述程序或者通过拆分外消旋混合物,由它们各自的光学活性前体制备。拆分可在拆分剂存在下通过色谱法或通过重复结晶或通过本领域技术人员已知的这些技术的一些组合来进行。有关拆分的另外细节可以在Jacques,et al.,Enantiomers,Racemates,and Resolutions(John Wiley&Sons,1981)中找到。当本文所述的化合物包含烯属双键、其他不饱和性或其他几何不对称中心时,并且除非另有说明,否则化合物意指包括E和Z几何异构体或者顺式和反式异构体两者。同样,也旨在包括所有互变异构形式。互变异构体可以是环状或非环状的。选择本文中出现的任何碳-碳双键的构型仅是为了方便起见,并不旨在指定具体的构型,除非本文如此陈述;因此,在本文中任意描述为反式的碳-碳双键或碳-杂原子双键可以是顺式、反式或二者的任何比例的混合物。

[0363] 本发明的某些化合物也可以以不同的稳定构象形式存在,其可以是可分离的。由于围绕不对称单键的旋转受限而引起的扭转不对称,例如由于位阻或环应变,可以允许不同构象异构体的分离。本发明包括这些化合物的每种构象异构体及其混合物。

[0364] 如本文所用,术语“药学上可接受的盐”是指在合理的医学判断范围内适合与人和低等动物的组织接触使用,而没有过度的毒性、刺激性、过敏反应等,并且相称地具有合理的益处/风险比的那些盐。药学上可接受的盐是本领域众所周知的。例如,S.M.Berge,et al.在J.Pharmaceutical Sciences,66:2-19(1977)中详细描述了药学上可接受的盐。这些盐可以在本发明的化合物的最终分离和纯化期间原位制备,或者通过游离碱官能团与合适的有机酸反应而分开制备。药学上可接受的盐的实例包括但不限于无毒酸加成盐,这些盐是用无机酸(诸如盐酸、氢溴酸、磷酸、硫酸和高氯酸)或用有机酸(诸如乙酸、马来酸、酒石酸、柠檬酸、琥珀酸或丙二酸)或者通过使用本领域使用的其他方法诸如离子交换形成的氨基基团的盐。其他药学上可接受的盐包括但不限于己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷-丙酸盐、二葡萄糖酸盐、十二烷基硫酸盐、乙磺酸盐、甲酸盐、富马酸盐、葡庚糖酸盐、甘油磷酸盐、葡萄糖酸盐、半硫酸盐、庚酸盐、己酸盐、氢碘酸盐、2-羟基-乙磺酸盐、乳糖醛酸盐、乳酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、马来酸盐、丙二酸盐、甲磺酸盐、2-萘磺酸盐、烟酸盐、硝酸盐、油酸盐、草酸盐、棕榈酸盐、双羟萘酸盐、果胶酸盐、过硫酸盐、3-苯基丙酸盐、磷酸盐、苦味酸盐、新戊酸盐、丙酸盐、硬脂酸盐、琥珀酸盐、硫酸盐、酒石酸盐、硫氰酸盐、对甲苯磺酸盐、十一酸盐、戊酸盐等。代表性的碱金属或碱土金属盐包括钠、锂、钾、钙、镁等。另外的药学上可接受的盐在适当时包括无毒的铵、季铵和胺阳离子,使用反荷离子诸如卤根、氢氧根、羧酸根、硫酸根、磷酸根、硝酸根、具有1至6个碳原子的烷基、磺酸根和芳基磺酸根形成。

[0365] 如本文所用,术语“药学上可接受的酯”是指在体内水解并包括在人体内容易分解而留下母体化合物或其盐的那些的酯。合适的酯基团包括例如衍生自药学上可接受的脂族

羧酸，特别是烷酸、烯酸、环烷酸和烷二酸的那些，其中每个烷基或烯基部分有利地具有不超过6个碳原子。具体酯的实例包括但不限于甲酸酯、乙酸酯、丙酸酯、丁酸酯、丙烯酸酯和乙基琥珀酸酯。

[0366] 药物组合物

[0367] 本发明的药物组合物包括与一种或多种药学上可接受的载体或赋形剂一起配制的治疗有效量的本发明的化合物。

[0368] 如本文所用，术语“药学上可接受的载体或赋形剂”意指任何类型的无毒、惰性固体、半固体或液体填充剂、稀释剂、包封材料或配制助剂。可以充当药学上可接受的载体的材料的一些实例是糖，诸如乳糖、葡萄糖和蔗糖；淀粉，诸如玉米淀粉和马铃薯淀粉；纤维素及其衍生物，诸如羧甲基纤维素钠、乙基纤维素和乙酸纤维素；粉末状黄芪胶；麦芽；明胶；滑石；赋形剂，诸如可可脂和栓剂蜡；油，诸如花生油、棉籽油；红花油；芝麻油；橄榄油；玉米油和大豆油；二醇，诸如丙二醇；酯，诸如油酸乙酯和月桂酸乙酯；琼脂；缓冲剂，诸如氢氧化镁和氢氧化铝；藻酸；无热原水；等渗盐水；林格溶液；乙醇和磷酸盐缓冲溶液，以及其他无毒的相容性润滑剂，诸如月桂基硫酸钠和硬脂酸镁，并且着色剂、脱模剂、包衣剂、甜味剂、调味剂和加香剂、防腐剂以及抗氧化剂根据配制者的判断也可以存在于组合物中。

[0369] 本发明的药物组合物可以口服、肠胃外，通过吸入喷雾、局部、直肠、经鼻、经颊、经阴道或经植入的容器给药，优选通过口服给药或通过注射给药。本发明的药物组合物可以包含任何常规的无毒的药学上可接受的载体、佐剂或媒介物。在一些情况下，可以用药学上可接受的酸、碱或缓冲剂调节制剂的pH，以增强所配制的化合物或其递送形式的稳定性。如本文所用，术语肠胃外包括皮下、皮内、静脉内、肌内、关节内、动脉内、滑膜内、胸骨内、鞘内、病灶内和颅内注射或输注技术。

[0370] 用于口服给药的液体剂型包括药学上可接受的乳剂、微乳剂、溶液、混悬剂、糖浆剂和酏剂。除活性化合物外，液体剂型还可包含本领域常用的惰性稀释剂，诸如例如水或其他溶剂，增溶剂和乳化剂，诸如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苄醇、苯甲酸苄酯、丙二醇、1,3-丁二醇、二甲基甲酰胺、油(尤其是棉籽油、落花生油、玉米油、胚芽油、橄榄油、蓖麻油和芝麻油)、甘油、四氢糠醇、聚乙二醇类和脱水山梨糖醇的脂肪酸酯以及其混合物。除惰性稀释剂外，口服组合物还可包括佐剂，诸如湿润剂、乳化剂和悬浮剂、甜味剂、调味剂和加香剂。

[0371] 可以根据已知技术使用合适的分散剂或湿润剂和悬浮剂来配制可注射制剂，例如无菌可注射水性或油性混悬剂。无菌可注射制剂也可以是在无毒的肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液、混悬剂或乳剂，例如作为在1,3-丁二醇中的溶液。可以采用的可接受的媒介物和溶剂是水、林格溶液、U.S.P.和等渗氯化钠溶液。另外，无菌的固定油常规地用作溶剂或悬浮介质。出于此目的，可以使用任何温和的固定油，包括合成的甘油单酯或甘油二酯。此外，脂肪酸诸如油酸用于制备可注射剂。

[0372] 可注射制剂可以通过以下灭菌，例如，通过细菌保留过滤器过滤，或以无菌固体组合物的形式掺入灭菌剂，其可以在使用前溶解或分散在无菌水或其他无菌可注射介质中。

[0373] 为了延长药物的作用，通常需要减缓皮下或肌内注射的药物吸收。这可以通过使用水溶性差的结晶或无定形材料的液体混悬剂来实现。然后，药物的吸收速率取决于其溶解速率，而溶解速率又可取决于晶体尺寸和结晶形式。替代地，通过将药物溶解或悬浮在油

媒介物中来实现肠胃外给药的药物形式的延迟吸收。通过在可生物降解的聚合物诸如聚丙交酯-聚乙交酯中形成药物的微胶囊基质来制备可注射的储库形式。取决于药物与聚合物的比率和所用具体聚合物的性质，可以控制药物释放速率。其他可生物降解的聚合物的实例包括聚(原酸酯)和聚(酸酐)。还通过将药物包埋在与身体组织相容的脂质体或微乳剂中来制备储库型可注射制剂。

[0374] 用于直肠或阴道给药的组合物优选地是栓剂，其可以通过将本发明的化合物与合适的无刺激性赋形剂或载体诸如可可脂、聚乙二醇或栓剂蜡混合来制备，其在环境温度下是固体，但在体温下是液体，并因此在直肠或阴道腔中融化并释放出活性化合物。

[0375] 用于口服给药的固体剂型包括胶囊剂、片剂、丸剂、散剂和颗粒剂。在此类固体剂型中，活性化合物与以下混合：至少一种惰性的药学上可接受的赋形剂或载体，诸如柠檬酸钠或磷酸二钙，和/或：a)填充剂或增量剂，诸如淀粉、乳糖、蔗糖、葡萄糖、甘露醇和硅酸，b)粘合剂，诸如例如羧甲基纤维素、藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖和阿拉伯胶，c)保湿剂，诸如甘油，d)崩解剂，诸如琼脂-琼脂、碳酸钙、马铃薯或木薯淀粉、藻酸、某些硅酸盐和碳酸钠，e)溶液阻滞剂，诸如石蜡，f)吸收促进剂，诸如季铵化合物，g)湿润剂，诸如例如鲸蜡醇和单硬脂酸甘油酯，h)吸收剂，诸如高岭土和膨润土黏土，以及i)润滑剂，诸如滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、月桂基硫酸钠，以及其混合物。在胶囊剂、片剂和丸剂的情况下，剂型还可包括缓冲剂。

[0376] 相似类型的固体组合物也可以用作软和硬填充明胶胶囊剂中的填充剂，其使用诸如乳糖(lactose)或乳糖(milk sugar)以及高分子量聚乙二醇类等的赋形剂。

[0377] 片剂、糖衣丸、胶囊剂、丸剂和颗粒剂的固体剂型可以用包衣和壳诸如肠溶衣和药物配制领域中众所周知的其他包衣来制备。它们可以任选地包含遮光剂，并且也可以是仅或优先地在肠道的某一部分中任选地以延迟方式释放一种或多种活性成分的组合物。可以使用的包埋组合物的实例包括聚合物物质和蜡。

[0378] 本发明的化合物的局部或经皮给药的剂型包括药膏、糊剂、乳膏、洗剂、凝胶剂、散剂、溶液、喷剂、吸入剂或贴剂。在无菌条件下将活性组分与可能需要的药学上可接受的载体和任何需要的防腐剂或缓冲剂混合。在本发明的范围内也考虑了眼科制剂、滴耳剂、眼药膏、散剂和溶液。

[0379] 除本发明的活性化合物外，药膏、糊剂、乳膏和凝胶剂还可包含赋形剂，诸如动物和植物脂肪、油、蜡、石蜡、淀粉、黄芪胶、纤维素衍生物、聚乙二醇类、硅酮、膨润土、硅酸、滑石和氧化锌或其混合物。

[0380] 除本发明的化合物外，散剂和喷剂还可包含赋形剂，诸如乳糖、滑石、硅酸、氢氧化铝、硅酸钙和聚酰胺粉末或这些物质的混合物。喷剂可以附加地包含常规推进剂，诸如氯氟烃。

[0381] 经皮贴剂具有向身体提供化合物的受控递送的附加优点。这样的剂型可以通过在适当的介质中溶解或分散化合物而制得。吸收增强剂也可以用来增加化合物穿过皮肤的通量。该速率可以通过提供速率控制膜或通过将化合物分散在聚合物基质或凝胶中来控制。

[0382] 对于肺递送，配制本发明的治疗组合物并通过直接给药例如吸入呼吸系统以固体或液体微粒形式向患者给药本发明的治疗组合物。制备用于实践本发明的活性化合物的固体或液体微粒形式包括呼吸性尺寸的颗粒：即，尺寸足够小以在吸入时通过口和喉并进入

肺支气管和肺泡的颗粒。雾化治疗剂,特别是雾化抗生素的递送是本领域已知的(参见例如Van Devanter等人的美国专利号5,767,068、Smith等人的美国专利号5,508,269和Montgomery的WO 98/43650,所有这些都通过援引并入本文)。

[0383] 联合和交替疗法

[0384] 已经认识到,在用抗病毒剂长期治疗后,可能出现HIV、HBV和HCV的耐药性变体。耐药性最典型地通过编码蛋白质的基因的突变发生,诸如用于病毒复制的酶,并且最典型地在HIV情况下的逆转录酶、蛋白酶或DNA聚合酶,以及在HBV的情况下的DNA聚合酶,或在HCV情况下的RNA聚合酶、蛋白酶或解旋酶。最近,已经证明,通过与诱导与主药导致的突变不同的突变的第二种,或者可能是第三种抗病毒化合物组合或交替给药化合物,可以延长、增强或恢复抗HIV感染的药物的功效。这些化合物可用于组合,其选自由HBV聚合酶抑制剂、干扰素、TLR调节剂诸如TLR-7激动剂或TLR-9激动剂、治疗性疫苗、某些细胞病毒RNA传感器的免疫激活剂、病毒进入抑制剂、病毒成熟抑制剂、不同的衣壳组装调节剂、不同或未知机制的抗病毒化合物及其组合组成的组。替代地,药物的药代动力学、生物分布或其他参数可通过这样的联合或交替疗法改变。一般地,联合疗法通常优于交替疗法,因为它对病毒诱导多个同时应激。

[0385] 用于治疗HBV的联合或交替疗法的优选化合物包括3TC、FTC、L-FMAU、干扰素、阿德福韦酯(adefovir dipivoxil)、恩替卡韦、替比夫定(telbivudine)(L-dT)、伐他滨(valtorcitabine)(3'-缬氨酰基L-dC)、β-D-二氧戊环基-鸟嘌呤(DXG)、β-D-二氧戊环基-2,6-二氨基嘌呤(DAPD)和β-D-二氧戊环基-6-氯嘌呤(ACP)、泛昔洛韦、喷昔洛韦(penciclovir)、洛布卡韦(lobucavir)、更昔洛韦和利巴韦林。

[0386] 尽管已经相对于各种优选实施方式对本发明进行了描述,但并不旨在限制于此,而本领域技术人员将认识到,在本发明的精神和所附权利要求的范围内,可以对其进行变化和修改。

[0387] 抗病毒活性

[0388] 本发明的化合物的抑制量或剂量范围可以为约0.01mg/Kg至约500mg/Kg,替代地为约1至约50mg/Kg。抑制量或剂量也将根据给药途径以及与其他剂共同使用的可能性而变化。

[0389] 根据本发明的治疗方法,通过以达到预期结果所需的这样的量和这样的时间向患者给药治疗有效量的本发明的化合物来治疗或预防患者诸如人或其他动物的病毒感染、病症。

[0390] 本发明的化合物的"治疗有效量"意指以适用于任何医学治疗的合理的益处/风险比赋予治疗受试者治疗效果的化合物的量。治疗效果可以是客观的(即,通过一些测试或标志可测量的)或主观的(即,受试者给出效果的迹象或感觉到效果)。有效量的上述化合物范围可以为约0.1mg/Kg至约500mg/Kg,优选约1至约50mg/Kg。有效剂量也将根据给药途径以及与其他剂共同使用的可能性而变化。然而,应该理解,本发明的化合物和组合物的总每日用量将由主治医师在合理的医学判断范围内决定。任何具体患者的特定治疗有效剂量水平将取决于多种因素,包括所治疗的疾患和疾患的严重程度;所用特定化合物的活性;所用的特定组合物;患者的年龄、体重、一般健康、性别和饮食;给药时间、给药途径和所用特定化合物的排泄率;治疗的持续时间;与所用特定化合物联合或同时使用的药物;以及医学领域

众所周知的类似因素。

[0391] 以单剂量或分剂量向人或其他动物给药的本发明的化合物的总每日剂量可以是例如0.01至50mg/kg体重或更通常0.1至25mg/kg体重的量。单剂量组合物可包含构成每日剂量的这样的量或其约数。通常，根据本发明的治疗方案包括每天以单剂量或多剂量向需要这样的治疗的患者给药约10mg至约1000mg的一种或多种本发明的化合物。

[0392] 本文所述的本发明的化合物可以，例如，通过静脉内、动脉内、真皮下、腹腔内、肌内或皮下注射给药；或口服、经颊、经鼻、经粘膜、局部、以眼科制剂或通过吸入给药，其中剂量范围为约0.1至约500mg/kg体重，替代地剂量为1mg至1000mg/剂，每4到120小时，或根据具体药物的要求。本文的方法考虑给药有效量的化合物或化合物组合物以实现期望的或所述的效果。通常，本发明的药物组合物将每天给药约1至约6次，或替代地作为连续输注给药。这样的给药可用作慢性或急性疗法。可以与药物赋形剂或载体组合以产生单一剂型的活性成分的量将根据所治疗的宿主和具体给药方式而变化。典型的制剂将包含约5％至约95％的活性化合物(w/w)。替代地，此类制剂可包含约20％至约80％的活性化合物。

[0393] 可能需要比上述剂量更低或更高的剂量。任何具体患者的特定剂量和治疗方案将取决于多种因素，包括所用特定化合物的活性、年龄、体重、一般健康状况、性别、饮食、给药时间、排泄率、药物组合、疾病、病症或症状的严重程度和病程、患者对疾病、病症或症状的处置以及治疗医师的判断。

[0394] 在改善患者病症后，如果需要，可以给药维持剂量的本发明的化合物、组合物或组合。随后，当症状已经缓解至期望水平时，可以随症状变化而将给药的剂量或频率或两者降低至保持改善的病症的水平。然而，一旦任何疾病症状复发时，患者可能需要长期间歇性治疗。

[0395] 当本发明的组合物包括本文所述的式的化合物与一种或多种附加的治疗剂或预防剂的组合时，化合物和附加的剂二者应当以在单一疗法方案中通常给药的剂量的约1至100％并且更优选地约5至95％的剂量水平存在。作为多剂量方案的一部分，附加的剂可以与本发明的化合物分开给药。替代地，这些剂可以是单一剂型的一部分，与单一组合物中的本发明的化合物混合在一起。

[0396] “附加的治疗剂或预防剂”包括但不限于免疫疗法(例如干扰素)，治疗性疫苗，抗纤维化剂，抗炎剂(诸如皮质类固醇或NSAID)，支气管扩张剂(诸如β-2肾上腺素能激动剂和黄嘌呤)(例如茶碱)，粘液溶解剂，抗毒蕈碱剂，抗白三烯，细胞粘附抑制剂(例如ICAM拮抗剂)，抗氧化剂(例如N-乙酰半胱氨酸)，细胞因子激动剂，细胞因子拮抗剂，肺表面活性剂和/或抗微生物剂和抗病毒制剂(例如利巴韦林和金刚烷胺(amantidine))。根据本发明的组合物还可以与基因替代疗法联用。

[0397] 缩写

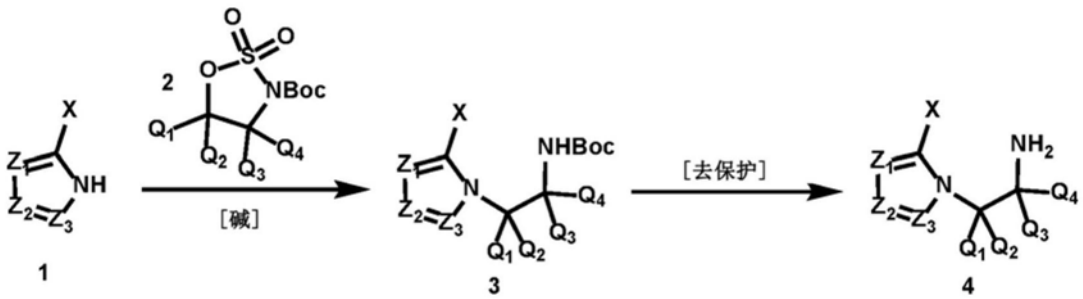
[0398] 在以下方案和实施例的描述中可以使用的缩写为：乙酰基为Ac；乙酸为AcOH；二碳酸二叔丁酯为Boc_2O；叔丁氧基羰基为Boc；苯甲酰基为Bz；苄基为Bn；叔丁醇钾为t-BuOK；氯化钠水溶液为盐水；羰基二咪唑为CDI；二氯甲烷为DCM或CH_2Cl_2；甲基为CH_3；乙腈为CH_3CN；碳酸铯为Cs_2CO_3；氯化铜(I)为CuCl；碘化铜(I)为CuI；二亚苄基丙酮为dba；1,8-二氮杂双环[5.4.0]-十一-7-烯为DBU；二乙基偶氮二甲酸酯为DEAD；偶氮二甲酸二异丙酯为DIAD；N,N-二异丙基乙胺为DIPEA或$(i\text{-}Pr)_2EtN$；1,1,2-三(乙酰氧基)-1,2-二氢-1,2-苯碘酰-3-

(1H)-酮为DMP或戴斯-马丁试剂(Dess-Martin periodinane);4-二甲基氨基-吡啶为DMAP;1,2-二甲氧基乙烷为DME;N,N-二甲基甲酰胺为DMF;二甲基亚砜为DMSO;乙酸乙酯为EtOAc;乙醇为EtOH;二乙醚为Et_2O;O-(7-氮杂苯并三唑-2-基)-N,N,N',N'-四甲基脲鎓六氟磷酸盐为HATU;氯化氢为HCl;碳酸钾为K_2CO_3;正丁基锂为n-BuLi;2,3-二氯-5,6-二氰基-1,4-苯醌为DDQ;二异丙基氨基锂为LDA;2,2,6,6-四甲基-哌啶酸锂为LiTMP;甲醇为MeOH;镁为Mg;甲氧基甲基为MOM;甲磺酰基或SO_2-CH_3为Ms;双(三甲基硅烷基)氨基钠为NaHMDS;氯化钠为NaCl;氢化钠为NaH;碳酸氢钠(sodium bicarbonate)或碳酸氢钠(sodium hydrogen carbonate)为$NaHCO_3$;碳酸钠为Na_2CO_3;氢氧化钠为NaOH;硫酸钠为Na_2SO_4;亚硫酸氢钠(sodium bisulfite)或亚硫酸氢钠(sodium hydrogen sulfite)为$NaHSO_3$;硫代硫酸钠为$Na_2S_2O_3$;肼为NH_2NH_2;氯化铵为NH_4Cl;镍为Ni;羟基为OH;四氧化锇为OsO_4;三氟甲磺酸酯为OTf;聚磷酸为PPA;对甲苯磺酸为PTSA;吡啶鎓对甲苯磺酸盐为PPTS;四丁基氟化铵为TBAF;三乙胺为TEA或Et_3N;三乙基硅烷基为TES;三乙基硅烷基氯化物为TESCl;三氟甲磺酸三乙基硅烷基酯为TESOTf;三氟乙酸为TFA;四氢呋喃为THF;N,N,N',N'-四甲基乙二胺为TMEDA;三苯基膦为TPP或PPh_3;甲苯磺酰基或-SO_2-$C_6H_4CH_3$为Tos或Ts;甲苯基磺酸酐或甲苯磺酰酐为Ts_2O;对甲苯基磺酸为TsOH;钯为Pd;苯基为Ph;三(二亚苄基丙酮)二钯(0)为$Pd_2(dba)_3$;四(三苯基膦)-钯(0)为$Pd(PPh_3)_4$;反式-二氯双(三苯基膦)钯(II)为$PdCl_2(PPh_3)_2$;铂为Pt;铑为Rh;室温为rt;钌为Ru;叔丁基二甲基硅烷基为TBS;三甲基硅烷基为TMS;或三甲基硅烷基氯化物为TMSCl。

[0399] 合成方法

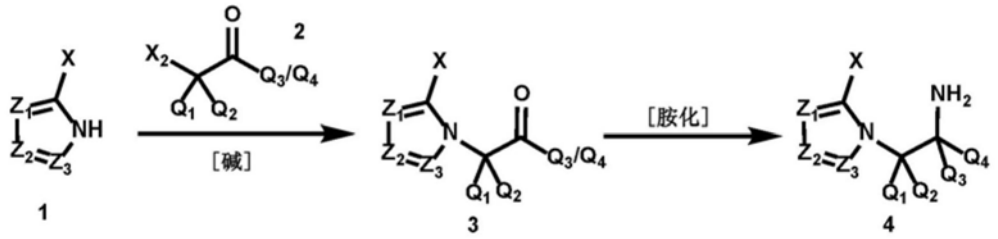
[0400] 结合以下合成方案将更好地理解本发明的化合物和方法,合成方案说明了可以制备本发明的化合物的方法。这些方案的目的是说明性的,并不意在限制本发明的范围。等效的、相似的或合适的溶剂、试剂或反应条件可以取代本文所述的那些具体溶剂、试剂或反应条件,而不脱离合成方法的一般范围。

[0401] 方案1:

[0402] 

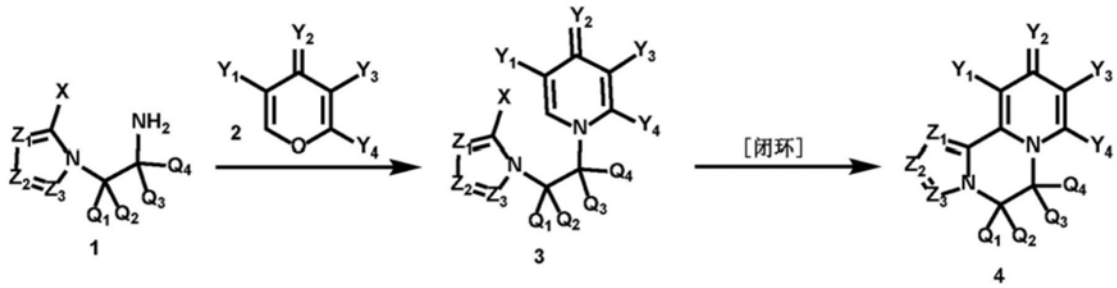
[0403] 在方案1中图示的,化合物诸如4(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3和Q_4如先前所定义;X定义为卤素)可以根据本文中图示的合成方法,或通过本领域技术人员已知的类似方法来制备。中间体1可以在碳-氮键形成反应中与磺胺内酯(sulfamidate)2反应,该反应通常由碱(表示为[碱])(包括但不限于:K_2CO_3、Cs_2CO_3、KOAc、NaOtBu、NaOH、KOH、NaH、Et_3N或DBU)介导。氨基甲酸酯3可以在去保护步骤(表示为[去保护])中使用试剂(包括但不限于:TFA、HCl或H_2SO_4)反应,以产生胺4。

[0404] 方案2:

[0405] 

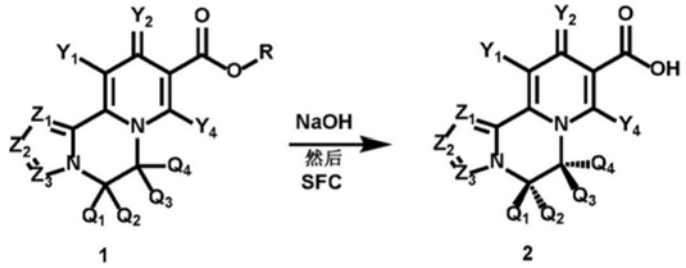
[0406] 在方案2中图示的，化合物诸如4(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3和Q_4如先前所定义；X定义为卤素)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。中间体1可以在碳-氮键形成反应中与酮2(X_2定义为卤素、-OTf、-OMs、-OAc或-OTs)反应，该反应通常由碱(表示为[碱])(包括但不限于：K_2CO_3、Cs_2CO_3、KOAc、NaOtBu、NaOH、KOH、Et_3N或DBU)介导。中间体3可以在胺化步骤(表示为[胺化])中使用试剂(包括但不限于：$NaBH_3CN$和NH_4OAc)反应以产生胺4。

[0407] 方案3：

[0408] 

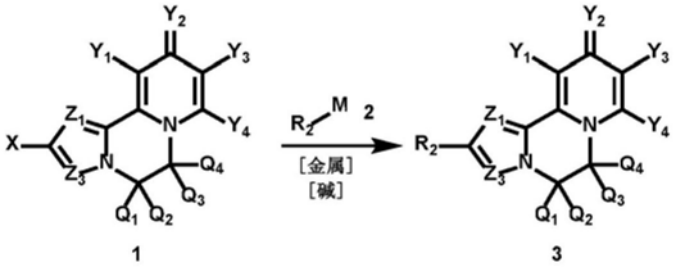
[0409] 在方案3中图示的，化合物诸如4(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2、Y_3和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。胺1(X定义为卤素)可以在缩合反应中与吡喃2反应以产生中间体3。中间体3可以在通常由含金属的试剂(包括但不限于：$Pd(OAc)_2$、$PdBr_2$或Pd-SPhos G3)和碱(包括但不限于：KOAc、K_2CO_3、Cs_2CO_3、Et_3N或K_3PO_4)介导的闭环步骤(表示为[闭环])中反应以产生杂环4。

[0410] 方案4：

[0411] 

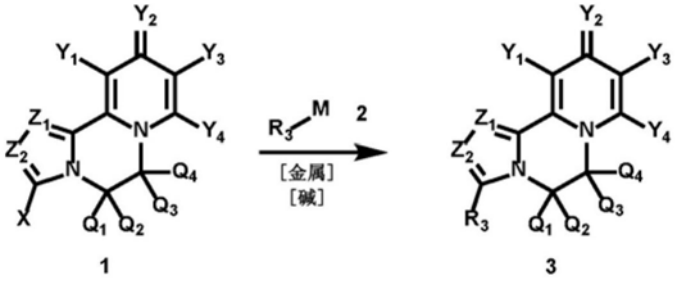
[0412] 在方案4中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。中间体1(R定义为氢、任选取代的C_2-C_6烷基或任选取代的芳基)可以在由NaOH介导的水解条件下反应，以及随后使用SFC纯化，可以获得具有高光学纯度的化合物诸如2。

[0413] 方案5：

[0414] 

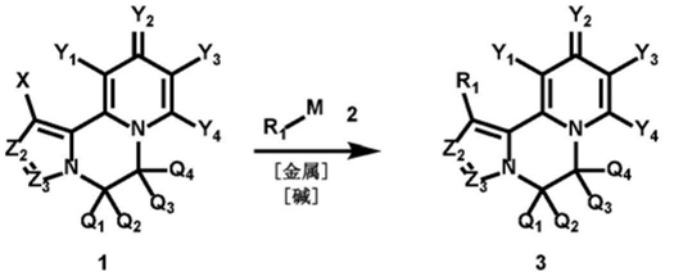
[0415] 在方案5中图示的，化合物诸如3(Z_1、Z_3、R_2、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2、Y_3和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。化合物1(X定义为卤素、-B(OH)$_2$、-BF_3K、-B(pin)、-OTf或-OMs)可以在偶联反应中与2(M定义为卤素、-B(OH)$_2$、-BF_3K、-B(pin)、-OTf或-OMs)反应以产生3，该反应由含金属的试剂(表示为[金属])(包括但不限于：包含Pd、Cu、Zn、Fe、Ir、Ru、Rh或Ni的试剂)和碱(表示为[碱])(包括但不限于：KOAc、K_2CO_3、Cs_2CO_3、Et_3N或K_3PO_4)介导。

[0416] 方案6：

[0417] 

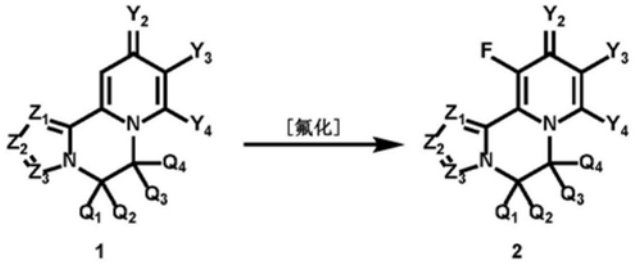
[0418] 在方案6中图示的，化合物诸如3(Z_1、Z_2、R_3、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2、Y_3和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。化合物1(X定义为卤素、-B(OH)$_2$、-BF_3K、-B(pin)、-OTf或-OMs)可以在偶联反应中与2(M定义为卤素、-B(OH)$_2$、-BF_3K、-B(pin)、-OTf或-OMs)反应以产生3，该反应由含金属的试剂(表示为[金属])(包括但不限于：包含Pd、Cu、Zn、Fe、Ir、Ru、Rh或Ni的试剂)和碱(表示为[碱])(包括但不限于：KOAc、K_2CO_3、Cs_2CO_3、Et_3N或K_3PO_4)介导。

[0419] 方案7：

[0420] 

[0421] 在方案7中图示的，化合物诸如3(Z_2、Z_3、R_1、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2、Y_3和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。化合物1(X定义为卤素、-B(OH)$_2$、-BF_3K、-B(pin)、-OTf或-OMs)可以在偶联反应中与2(M定义为卤素、-B(OH)$_2$、-BF_3K、-B(pin)、-OTf或-OMs)反应以产生3，该反应由含金属的试剂(表示为[金属])(包括但不限于：包含Pd、Cu、Zn、Fe、Ir、Ru、Rh或Ni的试剂)和碱(表示为[碱])(包括但不限于：KOAc、K_2CO_3、Cs_2CO_3、Et_3N或K_3PO_4)介导。

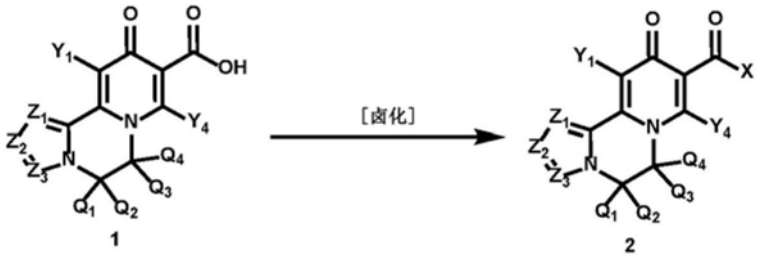
[0422] 方案8：

[0423] 

1 2

[0424] 在方案8中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_2、Y_3和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。1可以在氟化反应(表示为[氟化])中与亲电试剂(包括但不限于：NFSI或选择性氟试剂(SelectFluor))反应，以产生氟化化合物2。

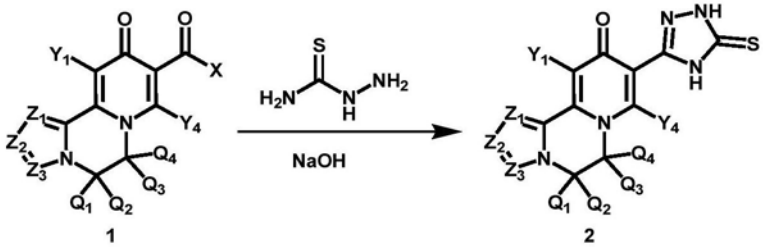
[0425] 方案9：

[0426] 

1 2

[0427] 在方案9中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；X定义为卤素)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酸1可以在卤化反应(表示为[卤化])中与亲电试剂(包括但不限于：$SOCl_2$、草酰氯、Ghosez试剂或$POBr_3$)反应，以产生酰卤2。

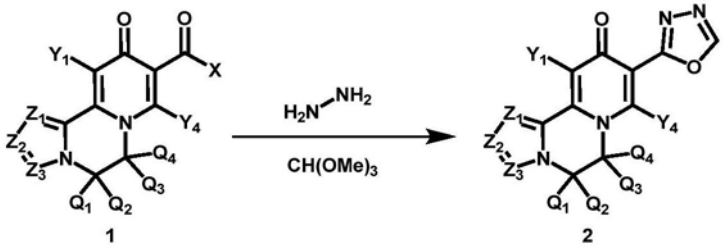
[0428] 方案10：

[0429] 

1 2

[0430] 在方案10中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在环化反应中与肼硫代甲酰胺(hydrazinecarbothioamide)和NaOH反应以产生2。

[0431] 方案11：

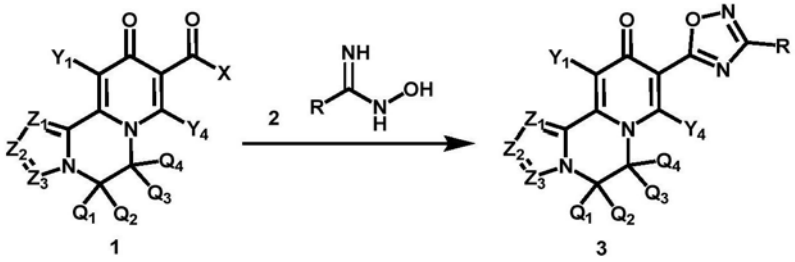
[0432] 

1 2

[0433] 在方案11中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可

以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在环化反应中与肼和原甲酸三甲酯反应以产生2。

[0434] 方案12：

[0435] 

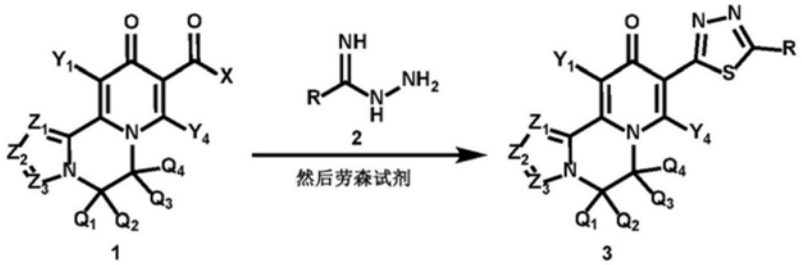
[0436] 在方案12中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在环化反应中与2反应以产生3。

[0437] 方案13：

[0438]

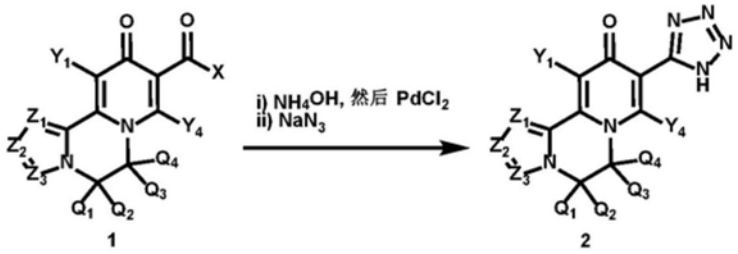
[0439] 在方案13中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在官能化反应中与氢氧化铵和氯化钯(II)反应以产生2。

[0440] 方案14：

[0441] 

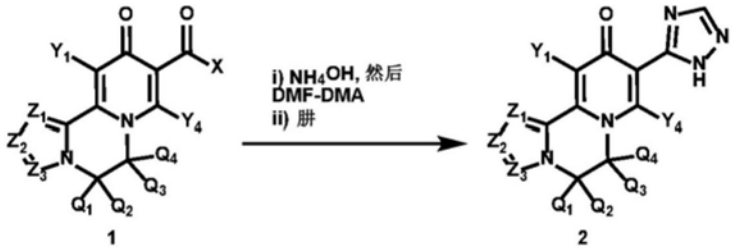
[0442] 在方案14中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在环化反应中与2反应，以及随后用劳森(Lawesson)试剂处理，产生化合物诸如3。

[0443] 方案15：

[0444] 

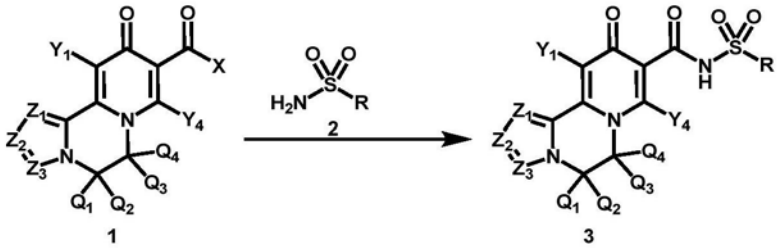
[0445] 在方案15中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在环化反应中与氢氧化铵和氯化钯(II)反应，随后与叠氮化钠反应，以产生2。_

[0446] 方案16：

[0447] 

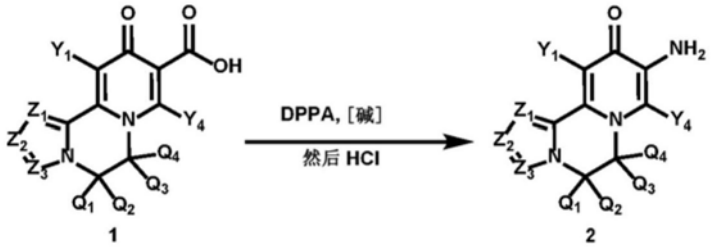
[0448] 在方案16中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在环化反应中与氢氧化铵和DMF-DMA反应，随后与肼反应，以产生2。

[0449] 方案17：

[0450] 

[0451] 在方案17中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酰卤1(X定义为卤素)可以在反应中与砜2反应以产生3。

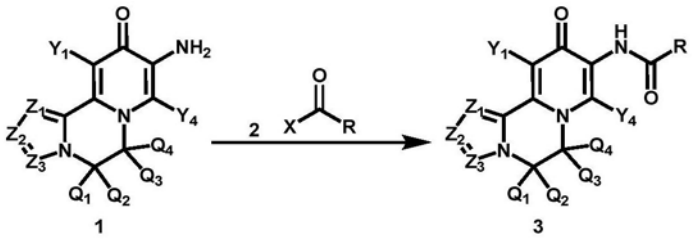
[0452] 方案18：

[0453] 

[0454] 在方案18中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酸1可以在重排反应中与DPPA、一种合适的碱(表示为[碱])(包括但不限于：Et_3N或Hunig碱)反应，以

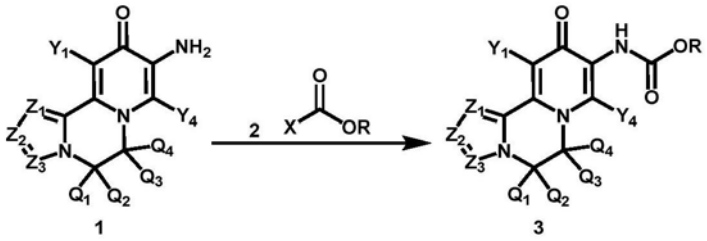
及随后与HCl反应，产生化合物诸如2。

[0455] 方案19：

[0456] 

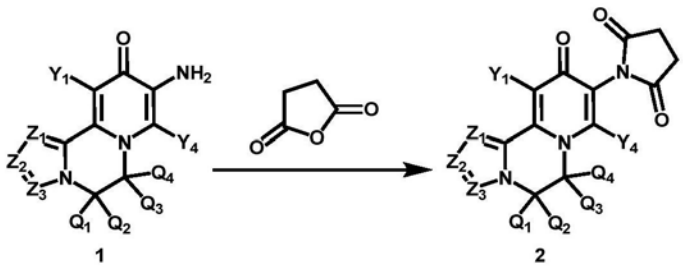
[0457] 在方案19中图示的，化合物诸如(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。胺1可以在反应中与酰卤2(X定义为卤素)反应以产生3。

[0458] 方案20：

[0459] 

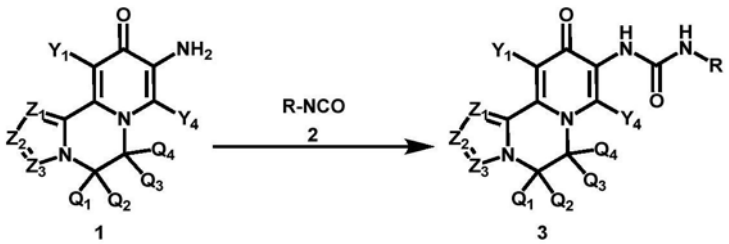
[0460] 在方案20中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。胺1可以在反应中与酰卤2(X定义为卤素)反应以产生3。

[0461] 方案21：

[0462] 

[0463] 在方案21中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。胺1可以在环化反应中与二氢呋喃-2,5-二酮反应以产生2。

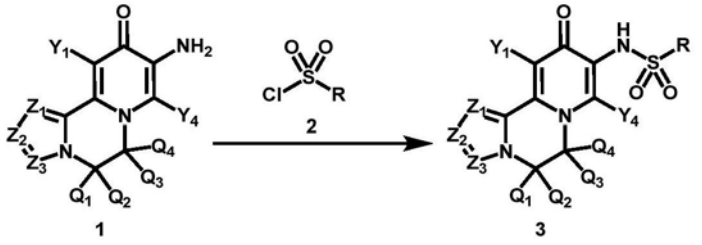
[0464] 方案22：

[0465] 

[0466] 在方案22中图示的，化合物诸如(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定

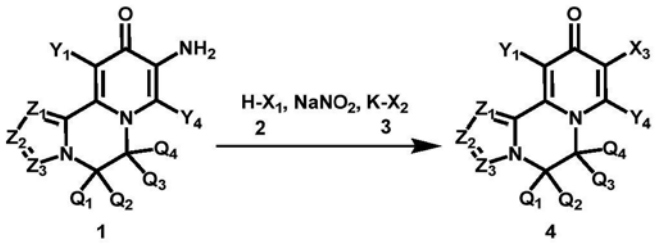
义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法,或通过本领域技术人员已知的类似方法来制备。胺1可以在反应中与异氰酸酯2反应以产生3。

[0467] 方案23:

[0468] 

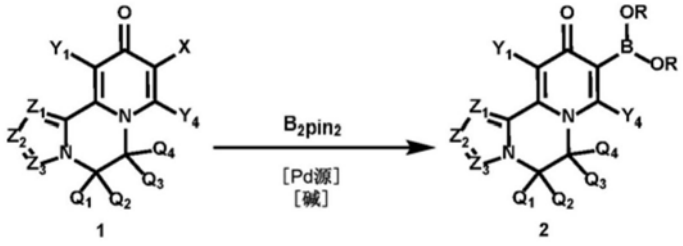
[0469] 在方案23中图示的,化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义;R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法,或通过本领域技术人员已知的类似方法来制备。胺1可以在反应中与磺酰氯2反应以产生3。

[0470] 方案24:

[0471] 

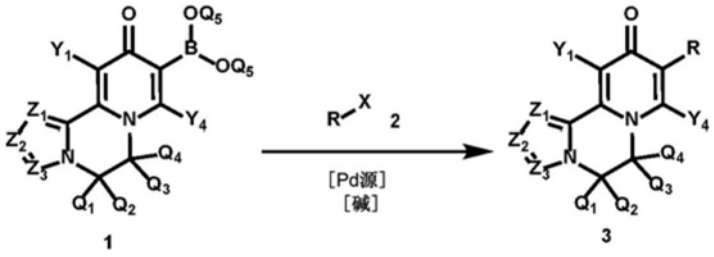
[0472] 在方案24中图示的,化合物诸如4(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义;X_3定义为卤素)可以根据本文中图示的合成方法,或通过本领域技术人员已知的类似方法来制备。胺1可以在桑德迈尔(Sandmeyer)型反应中与质子化合物2(X_1定义为卤素)、亚硝酸钠和钾盐(X_2定义为卤素)反应以产生4。

[0473] 方案25:

[0474] 

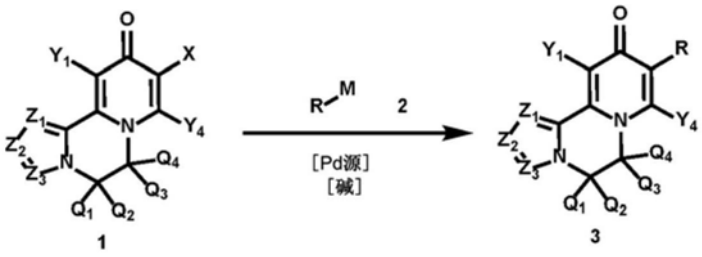
[0475] 在方案25中图示的,化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义;每个R独立地定义为氢或任选取代的烷基;替代地,R基团可以组合以形成任选取代的杂环)可以根据本文中图示的合成方法,或通过本领域技术人员已知的类似方法来制备。卤化物1可以在通常由含Pd试剂(表示为[Pd源])(包括但不限于:$Pd(OAc)_2$、$PdCl_2(dppf)$或$Pd(PPh_3)_4$)和碱(表示为[碱])(包括但不限于:KOAc、K_2CO_3或Et_3N)介导的硼基化反应中反应以产生2。

[0476] 方案26:

[0477] 

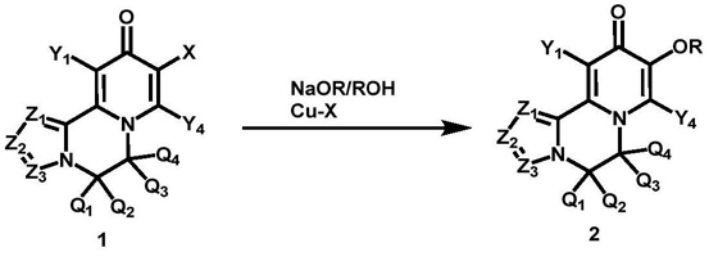
[0478] 在方案26中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。含硼的中间体1(每个Q_5独立地定义为氢或任选取代的烷基；替代地，R基团可以组合以形成任选取代的杂环)可以在偶联反应中与卤化物2(X定义为卤素)反应以产生3，该反应通常由含Pd试剂(表示为[Pd源])(包括但不限于：$Pd(OAc)_2$、$PdCl_2(dppf)$或$Pd(PPh_3)_4$)和碱(表示为[碱])(包括但不限于：KOAc、K_2CO_3或Et_3N)介导。

[0479] 方案27：

[0480] 

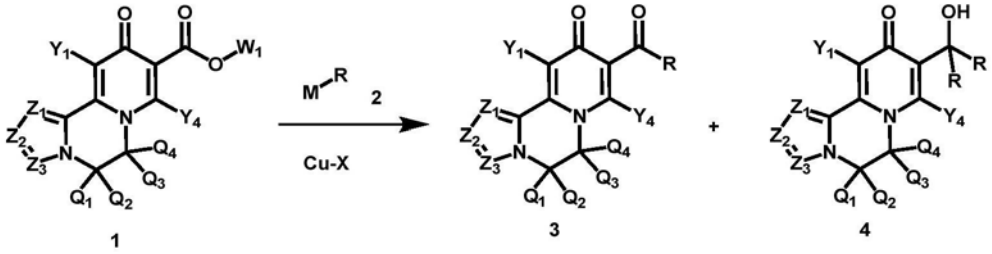
[0481] 在方案27中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。卤化物1(X定义为卤素)可以在通常由含Pd试剂(表示为[Pd源])(包括但不限于：$Pd(OAc)_2$、$PdCl_2(dppf)$或$Pd(PPh_3)_4$)和碱(表示为[碱])(包括但不限于：KOAc、K_2CO_3或Et_3N)介导的偶联反应中与2(M定义为包含以下原子的官能团，该原子包括但不限于：B、Sn、Al、Si、Zn或Mg)反应以产生3。

[0482] 方案28：

[0483] 

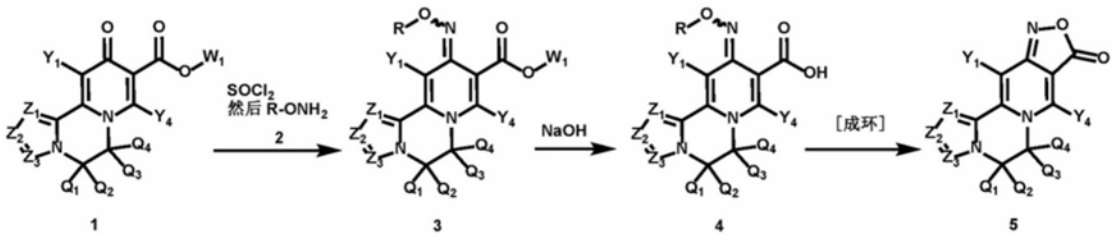
[0484] 在方案28中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；R定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。卤化物1(X定义为卤素)可以在偶联反应中与含Cu试剂(包括但不限于：CuBr或CuI)和醇及其共轭碱(即NaOR/ROH)反应以产生3。

[0485] 方案29：

[0486] 

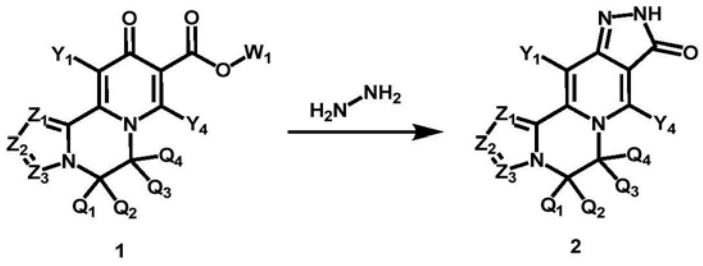
[0487] 在方案29中图示的，化合物诸如3和/或4(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义；每个R独立地定义为任选取代的烷基、任选取代的芳基、任选取代的杂环基或任选取代的杂芳基)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酯1(W_1定义为任选取代的烷基)可以在通常由含Cu试剂(包括但不限于：CuI或CuBr)介导的取代反应中与2(M定义为包含以下原子的官能团，该原子包括但不限于：B、Sn、Al、Si、Zn或Mg)反应以产生3和/或4。

[0488] 方案30：

[0489] 

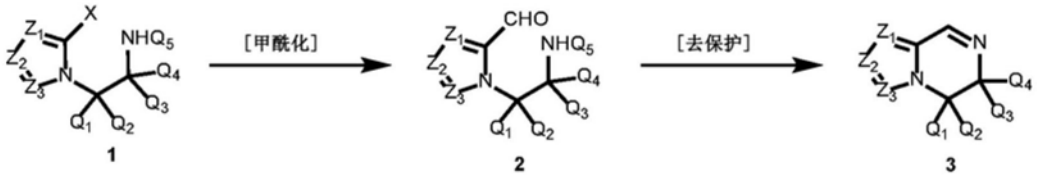
[0490] 在方案30中图示的，化合物诸如5(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酯1(W_1定义为任选取代的烷基)可以被亚硫酰氯活化，然后与胺2(R定义为氢或任选取代的烷基)反应以产生肟3。这可以用NaOH进行皂化以产生酸4。该中间体可以在环化反应(表示为[成环])中反应以产生5。

[0491] 方案31：

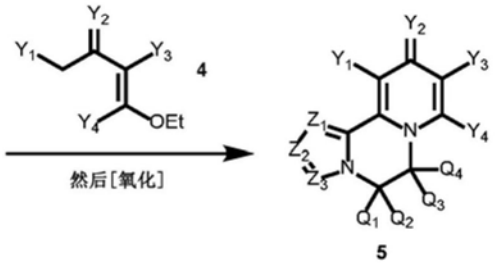
[0492] 

[0493] 在方案31中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酯1(W_1定义为任选取代的烷基)可以在环化反应中与肼反应以产生2。

[0494] 方案32：



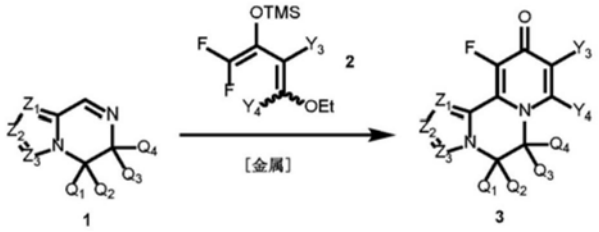
[0495]



[0496] 在方案32中图示的，化合物诸如5(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2、Y_3和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。唑1(X定义为卤素，Q_5定义为基于碳的保护基团，包括但不限于：Boc或三苯甲基)可以在甲酰化反应(在方案32中表示为[甲酰化])中反应以产生醛2，该反应由强碱(包括但不限于：异丙基镁氯化物或LDA)介导。这可以在由酸性试剂(包括但不限于：TFA或HCl)介导的去保护反应(在方案32中表示为[去保护])中反应以产生中间体3。这可以与化合物4反应以生成中间体环加成物，该中间体环加成物可以被氧化(在方案32中表示为[氧化])以产生吡啶酮5。

[0497] 方案33：

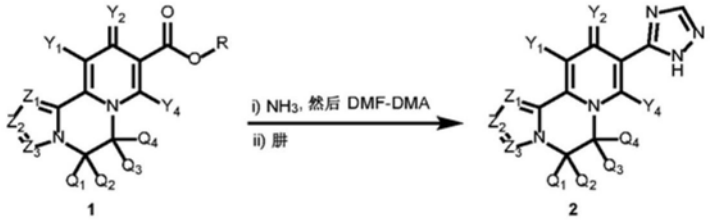
[0498]



[0499] 在方案33中图示的，化合物诸如3(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_3和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。唑1可以与中间体2反应成环以产生吡啶酮3，该反应由基于金属的试剂(在方案33中表示为[金属])(包括但不限于：ZnI_2、$ZnBr_2$或$ZnCl_2$)介导。

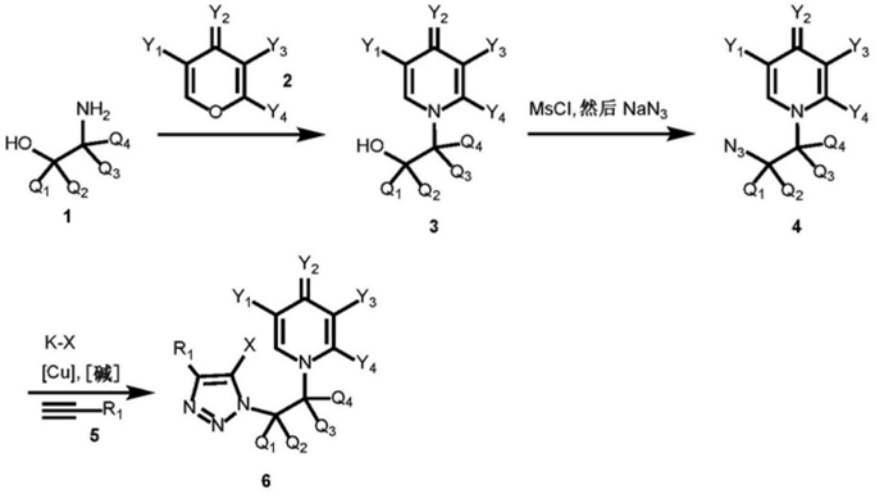
[0500] 方案34：

[0501]



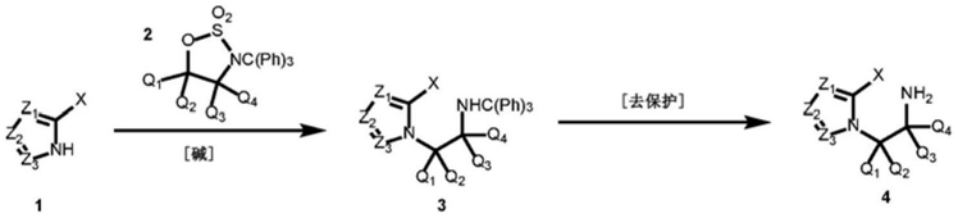
[0502] 在方案34中图示的，化合物诸如2(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2和Y_4如先前所定义)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。酯1(R定义为任选取代的烷基)可以与氨反应，然后与DMF-DMA反应。与肼反应之后，可以产生三唑2。

[0503] 方案35：

[0504] 

[0505] 在方案35中图示的，化合物诸如6(R_1、Q_1、Q_2、Q_3、Q_4、Y_1、Y_2、Y_3和Y_4如先前所定义；X定义为卤素)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。氨基醇1可以与吡喃2缩合以产生中间体3。醇官能可以用MsCl活化，然后用NaN_3取代以产生叠氮化物4。这可以与炔烃5进行环加成反应以产生三唑6，该反应由钾盐、铜试剂(在方案35中表示为[Cu])(包括但不限于：$CuCl_2$、$Cu(OAc)_2$或$Cu(ClO_4)_2$六水合物)和碱(在方案35中表示为[碱])(包括但不限于：Et_3N、DBU或DIPEA)介导。

[0506] 方案36：

[0507] 

[0508] 在方案36中图示的，化合物诸如4(Z_1、Z_2、Z_3、Q_1、Q_2、Q_3和Q_4如先前所定义；X定义为卤素)可以根据本文中图示的合成方法，或通过本领域技术人员已知的类似方法来制备。中间体1可以在碳-氮键形成反应中与磺胺内酯2反应，该反应通常由碱(表示为[碱])(包括但不限于：K_2CO_3、Cs_2CO_3、KOAc、NaOtBu、NaOH、KOH、NaH、Et_3N或DBU)介导。胺3可以在去保护步骤(表示为[去保护])中使用试剂(包括但不限于：TFA、HCl或H_2SO_4)反应，以产生胺4。

[0509] 本文引用的所有参考文献，无论是印刷版、电子版、计算机可读存储介质还是其他形式，均通过援引以其整体明确地并入，包括但不限于摘要、文章、期刊、出版物、教科书、论文、因特网网站、数据库、专利和专利出版物。

[0510] 对于所公开的实施方式的各种改变和修改对于本领域技术人员将是显而易见的，并且可以进行这样的改变和修改，包括但不限于与本发明的化学结构、取代基、衍生物、制剂和/或方法有关的那些改变和修改，而不背离本发明的精神和所附权利要求的范围。

[0511] 尽管已经相对于各种优选实施方式对本发明进行了描述，但并不旨在限制于此，而本领域技术人员将认识到，在本发明的精神和所附权利要求的范围内，可以对其进行变化和修改。

[0512] 实施例

[0513] 结合以下实施例将更好地理解本发明的化合物和方法，其仅旨在为说明，并不限

制本发明的范围。起始材料从商业供应商可获得或通过本领域技术人员众所周知的方法产生。

[0514] 通用条件：

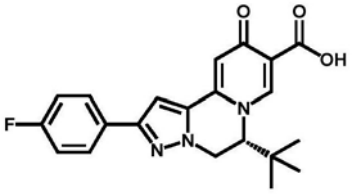
[0515] 使用电喷雾电离在LC-MS系统上运行质谱。这些是具有Agilent 6120四极检测器的Agilent 1290Infinity II系统。使用ZORBAX Eclipse XDB-C18柱(4.6x30mm,1.8微米)获得谱。使用水中的0.1％甲酸(A)和乙腈中的0.1％甲酸(B)的流动相在298K下获得谱。用以下溶剂梯度获得谱:0-1.5min:5％(B)、1.5-4.5min:5-95％(B)以及4.5-6min:95％(B)。溶剂流速为1.2mL/min。在210nm和254nm波长下检测化合物。$[M+H]^+$是指单一同位素分子量。

[0516] 在Bruker 400MHz谱仪上运行NMR谱。谱在298K下测量,并使用溶剂峰参考。^1H NMR的化学位移以百万分率(ppm)报告。

[0517] 使用Gilson GX-281自动化液体处理系统,通过反相高效液相色谱法(RPHPLC)纯化化合物。除非另有说明,否则化合物在Phenomenex Kinetex EVO C18柱(250x21.2mm,5微米)上纯化。除非另有说明,否则使用水(A)和乙腈(B)的流动相,使用0％至100％(B)的梯度洗脱,在298K下纯化化合物。溶剂流速为20mL/min,并在254nm波长下检测化合物。

[0518] 替代地,使用Teledyne ISCO Combiflash纯化系统通过正相液相色谱法(NPLC)纯化化合物。将化合物在REDISEP硅胶柱上纯化。将化合物在298K下纯化,并在254nm波长下检测。

[0519] 实施例1:合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0520] 

[0521] 步骤1:在烘箱干燥的烧瓶中装入3,5-二溴-1H-吡唑(3g,13.28mmol)和THF(30mL)。将反应混合物在冰浴中冷却,并向其中添加氢化钠(584mg,14.61mmol)。在该温度下搅拌20分钟之后,添加在THF(20mL)中呈溶液的(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷(oxathiazolidine)-3-甲酸叔丁酯2,2-二氧化物(4.45g,15.94mmol)的溶液。然后将反应混合物温热至室温。6h之后,添加MeOH(1mL),然后去除挥发物。将残余物溶解在DCM(50mL)中,然后添加TFA(10mL)。在室温下搅拌14h之后,去除挥发物,并且粗产物无需进一步纯化即用于下一步骤。ESI MS m/z＝326.1$[M+H]^+$。

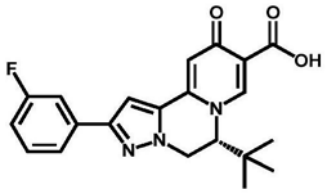
[0522] 步骤2:将来自前一步骤的材料溶解在2:1EtOH:AcOH(25mL)中。向其中添加在EtOH(10mL)中呈溶液的4-氧亚基-4H-吡喃-3-甲酸乙酯(3.34g,19.84mmol)的溶液。将反应混合物加热至回流持续18h,然后使其达到室温。去除挥发物,并将残余物在硅胶上用0-15％MeOH:EtOAc纯化以得到(R)-2-(2-(3,5-二溴-1H-吡唑-2-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(3.5g,三个步骤的产率为57％)。ESI MS m/z＝476.1$[M+H]^+$。

[0523] 步骤3:在烘箱干燥的小瓶中装入(R)-2-(2-(3,5-二溴-1H-吡唑-2-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(3g,6.31mmol)、$PdBr_2$(168mg,

0.631mmol)、KOAc(929mg,9.47mmol)以及DMF(25mL)。将反应混合物在90℃下搅拌14h。然后,去除DMF,并将残余物在硅胶上用0-15%MeOH:EtOAc纯化以得到(R)-2-溴-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸乙酯(1.3g,52%产率)。ESI MS m/z=395.1[M+H]$^+$。

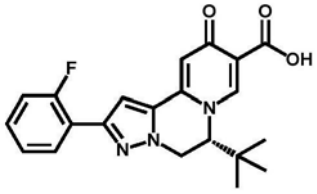
[0524] 步骤4:在烘箱干燥的小瓶中装入(R)-2-溴-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸乙酯(25mg,0.063mmol)、(4-氟苯基)硼酸(9mg,0.063mmol)、Cs_2CO_3(62mg,0.19mmol)以及Pd-XPhos-G3(7mg,0.006mmol)。用氮气吹扫小瓶,然后添加1,4-二噁烷(2mL)和水(1mL)。将反应混合物在100℃下加热持续16h,然后使其达到室温。将反应混合物用DCM(5mL)稀释并将pH用1M的HCl水溶液调节至3。用DCM(3x5mL)萃取产物,并将合并的有机层浓缩。将残余物通过RP-HPLC纯化以得到(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(2mg,12%产率)。ESI MS m/z=382.1[M+H]$^+$。

[0525] 实施例2:合成(R)-6-(叔丁基)-2-(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0526] 

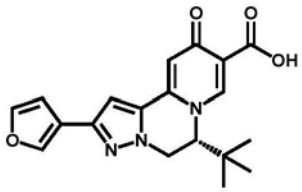
[0527] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(2mg)。ESI MS m/z=382.1[M+H]$^+$。

[0528] 实施例3:合成(R)-6-(叔丁基)-2-(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0529] 

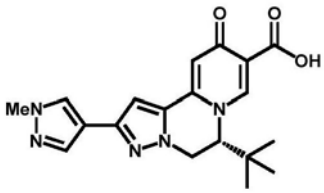
[0530] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(2.6mg)。ESI MS m/z=382.1[M+H]$^+$。

[0531] 实施例4:合成(R)-6-(叔丁基)-2-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0532] 

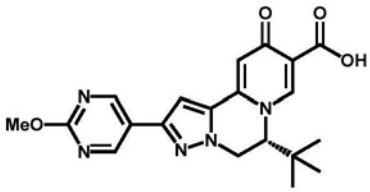
[0533] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用呋喃-3-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝354.1[M+H]$^+$。

[0534] 实施例5:合成(R)-6-(叔丁基)-2-(2-甲基-1H-吡唑-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0535] 

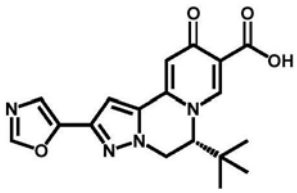
[0536] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用2-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)-1H-吡唑代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-甲基-1H-吡唑-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.9mg)。ESI MS m/z＝368.1[M+H]$^+$。

[0537] 实施例6:合成(R)-6-(叔丁基)-2-(2-甲氧基嘧啶-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0538] 

[0539] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-甲氧基嘧啶-5-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-甲氧基嘧啶-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝396.1[M+H]$^+$。

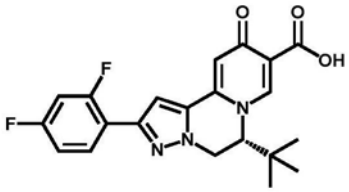
[0540] 实施例7:合成(R)-6-(叔丁基)-2-(噁唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0541] 

[0542] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚

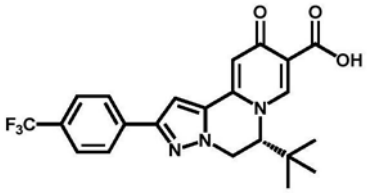
基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用5-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)噁唑代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(噁唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝355.1[M+H]$^+$。

[0543] 实施例8:合成(R)-6-(叔丁基)-2-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0544] 

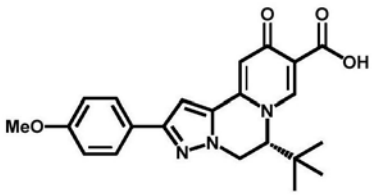
[0545] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,4-二氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝400.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.46(s,1H),8.61(s,1H),8.00(td,J＝8.6,6.4Hz,1H),7.10(d,J＝3.3Hz,1H),7.02(s,1H),7.01-6.89(m,2H),4.94(d,J＝14.2Hz,1H),4.69(dd,J＝13.8,3.8Hz,1H),4.29(d,J＝4.7Hz,1H),0.91(s,9H)。

[0546] 实施例9:合成(R)-6-(叔丁基)-10-氧亚基-2-(4-(三氟甲基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0547] 

[0548] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(4-(三氟甲基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(4-(三氟甲基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝432.1[M+H]$^+$。

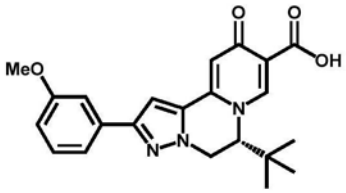
[0549] 实施例10:合成(R)-6-(叔丁基)-2-(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0550] 

[0551] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(4-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。

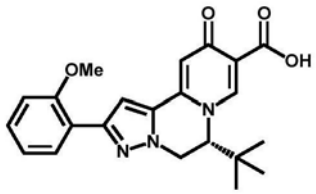
ESI MS m/z＝394.1[M+H]$^+$。

[0552] 实施例11:合成(R)-6-(叔丁基)-2-(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0553] 

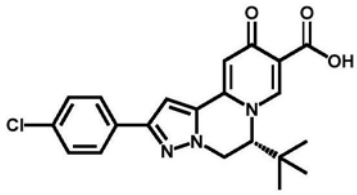
[0554] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝394.1[M+H]$^+$。

[0555] 实施例12:合成(R)-6-(叔丁基)-2-(2-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0556] 

[0557] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝394.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.59(s,1H),8.58(s,1H),7.99(dd,J＝7.7,1.8Hz,1H),7.35(ddd,J＝8.4,7.3,1.8Hz,1H),7.28(s,1H),7.07-6.98(m,3H),4.92(d,J＝14.3Hz,1H),4.68(dd,J＝14.4,5.0Hz,1H),4.27(d,J＝4.8Hz,1H),3.95(s,3H),0.89(s,9H)。

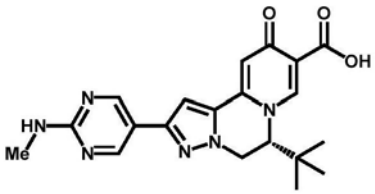
[0558] 实施例13:合成(R)-6-(叔丁基)-2-(4-氯苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0559] 

[0560] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(4-氯苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(4-氯苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝398.1[M+H]$^+$。

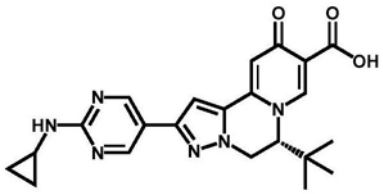
[0561] 实施例14:合成(R)-6-(叔丁基)-2-(2-(甲基氨基)嘧啶-5-基)-10-氧亚基-5,6-

二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0562] 

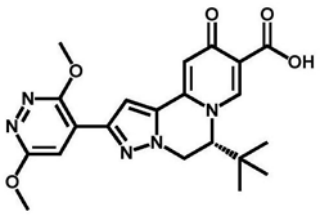
[0563] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(甲基氨基)嘧啶-5-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(甲基氨基)嘧啶-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.1mg)。ESI MS m/z＝395.1[M+H]$^+$。

[0564] 实施例15:合成(R)-6-(叔丁基)-2-(2-(环丙基氨基)嘧啶-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0565] 

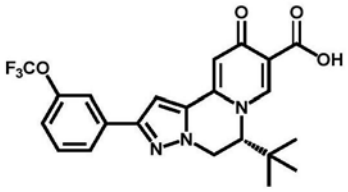
[0566] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(环丙基氨基)嘧啶-5-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(环丙基氨基)嘧啶-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.1mg)。ESI MS m/z＝421.1[M+H]$^+$。

[0567] 实施例16:合成(R)-6-(叔丁基)-2-(3,6-二甲氧基哒嗪-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0568] 

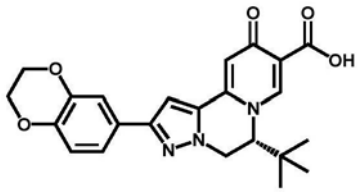
[0569] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3,6-二甲氧基哒嗪-4-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(3,6-二甲氧基哒嗪-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝426.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.32(s,1H),8.56(s,1H),7.60(s,1H),7.41(s,1H),7.05(s,1H),4.95(d,J＝14.2Hz,1H),4.69(d,J＝14.4Hz,1H),4.27-4.23(m,1H),4.22(s,3H),4.10(s,3H),0.90(s,9H)。

[0570] 实施例17:合成(R)-6-(叔丁基)-10-氧亚基-2-(3-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0571] 

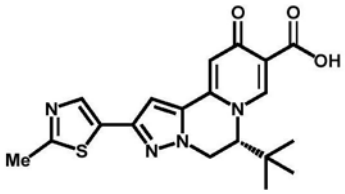
[0572] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3-(三氟甲氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(3-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.9mg)。ESI MS m/z＝448.1[M+H]$^+$。

[0573] 实施例18:合成(R)-6-(叔丁基)-2-(2,3-二氢苯并[b][1,4]二噁英-6-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0574] 

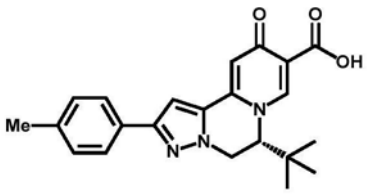
[0575] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,3-二氢苯并[b][1,4]二噁英-6-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,3-二氢苯并[b][1,4]二噁英-6-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝422.1[M+H]$^+$。

[0576] 实施例19:合成(R)-6-(叔丁基)-2-(2-甲基噻唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0577] 

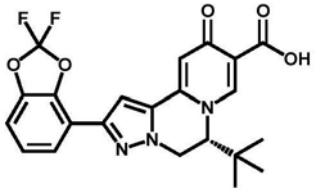
[0578] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-甲基噻唑-5-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-甲基噻唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.1mg)。ESI MS m/z＝385.1[M+H]$^+$。

[0579] 实施例20:合成(R)-6-(叔丁基)-10-氧亚基-2-(对甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0580] 

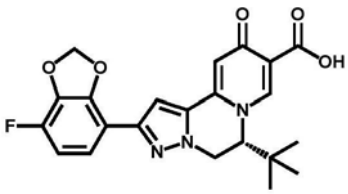
[0581] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用对甲苯基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(对甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z=378.1[M+H]$^+$。

[0582] 实施例21:合成(R)-6-(叔丁基)-2-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0583] 

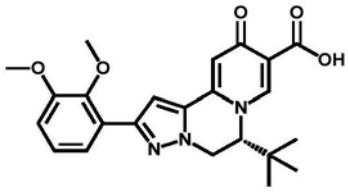
[0584] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.9mg)。ESI MS m/z=444.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.44(s,1H),8.62(s,1H),7.71(dd,J=8.2,1.2Hz,1H),7.19-7.13(m,2H),7.09-7.05(m,2H),4.97(d,J=14.4Hz,1H),4.72(dd,J=14.5,5.0Hz,1H),4.32(d,J=4.9Hz,1H),0.91(s,9H)。

[0585] 实施例22:合成(R)-6-(叔丁基)-2-(7-氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0586] 

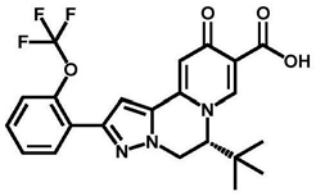
[0587] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(7-氟苯并[d][1,3]二氧杂环戊烯-4-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(7-氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z=426.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.40(s,1H),8.55(s,1H),7.42(dd,J=9.0,4.8Hz,1H),7.13(s,1H),7.01(s,1H),6.77(t,J=9.2Hz,1H),6.22-6.15(m,2H),4.94(d,J=14.4Hz,1H),4.67(dd,J=14.4,5.1Hz,1H),4.22(d,J=5.0Hz,1H),0.90(s,9H)。

[0588] 实施例23:合成(R)-6-(叔丁基)-2-(2,3-二甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0589] 

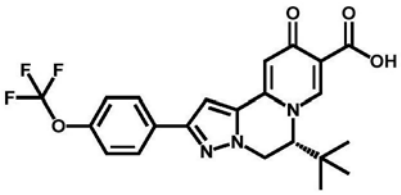
[0590] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,3-二甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,3-二甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.9mg)。ESI MS m/z＝424.1[M+H]$^+$。

[0591] 实施例24:合成(R)-6-(叔丁基)-10-氧亚基-2-(2-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0592] 

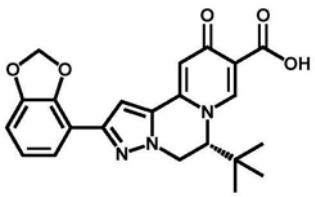
[0593] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(三氟甲氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(2-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.1mg)。ESI MS m/z＝448.1[M+H]$^+$。

[0594] 实施例25:合成(R)-6-(叔丁基)-10-氧亚基-2-(4-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0595] 

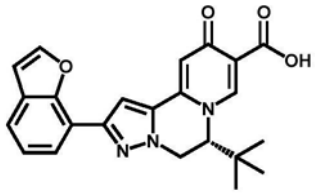
[0596] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(4-(三氟甲氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(4-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝448.1[M+H]$^+$。

[0597] 实施例26:合成(R)-2-(苯并[d][1,3]二氧杂环戊烯-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0598] 

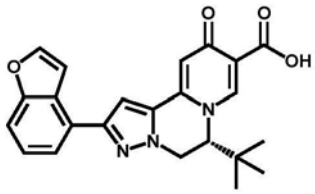
[0599] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用苯并[d][1,3]二氧杂环戊烯-4-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(苯并[d][1,3]二氧杂环戊烯-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝408.1[M+H]$^+$。

[0600] 实施例27:合成(R)-2-(苯并呋喃-7-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0601] 

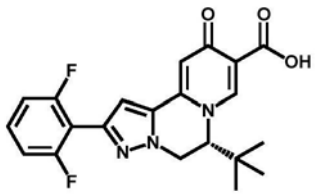
[0602] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用苯并呋喃-7-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(苯并呋喃-7-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.2mg)。ESI MS m/z＝404.1[M+H]$^+$。

[0603] 实施例28:合成(R)-2-(苯并呋喃-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0604] 

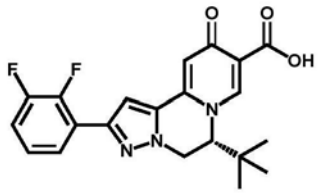
[0605] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用苯并呋喃-4-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(苯并呋喃-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝404.1[M+H]$^+$。

[0606] 实施例29:合成(R)-6-(叔丁基)-2-(2,6-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0607] 

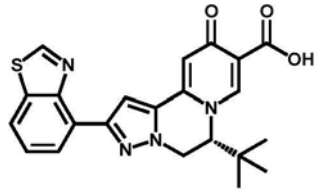
[0608] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,6-二氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,6-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝400.1[M+H]$^+$。

[0609] 实施例30:合成(R)-6-(叔丁基)-2-(2,3-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0610] 

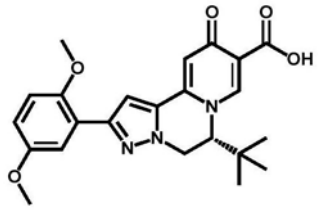
[0611] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,3-二氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,3-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z=400.1[M+H]$^+$。

[0612] 实施例31:合成(R)-2-(苯并[d]噻唑-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0613] 

[0614] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用苯并[d]噻唑-4-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(苯并[d]噻唑-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z=421.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.50(s,1H),9.13(s,1H),8.56(s,1H),8.22(dd,J=7.6,1.2Hz,1H),8.00(dd,J=8.0,1.2Hz,1H),7.97(s,1H),7.54(t,J=7.8Hz,1H),7.12(s,1H),5.00(d,J=14.3Hz,1H),4.73(dd,J=14.4,4.9Hz,1H),4.23(d,J=4.7Hz,1H),0.93(s,9H)。

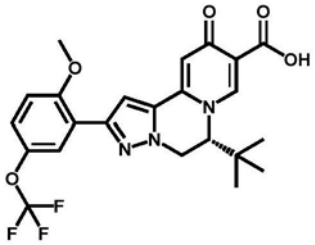
[0615] 实施例32:合成(R)-6-(叔丁基)-2-(2,5-二甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0616] 

[0617] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,5-二甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,5-二甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z=424.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.47(s,1H),8.51(s,1H),7.58(d,J=2.9Hz,1H),7.31(s,1H),7.03(s,1H),6.97-6.87(m,2H),4.94(d,J=14.3Hz,

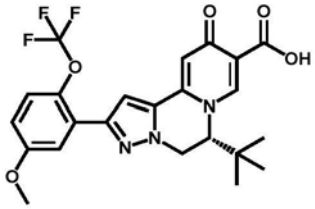
1H),4.65(dd,J＝14.4,5.0Hz,1H),4.17(d,J＝4.7Hz,1H),3.90(s,3H),3.85(s,3H),0.91(s,9H)。

[0618] 实施例33:合成(R)-6-(叔丁基)-2-(2-甲氧基-5-(三氟甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0619] 

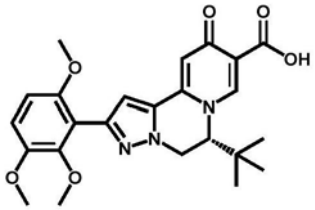
[0620] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-甲氧基-5-(三氟甲氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-甲氧基-5-(三氟甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝478.1[M+H]$^+$。

[0621] 实施例34:合成(R)-6-(叔丁基)-2-(5-甲氧基-2-(三氟甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0622] 

[0623] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-乙氧基-5-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(5-甲氧基-2-(三氟甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝478.1[M+H]$^+$。

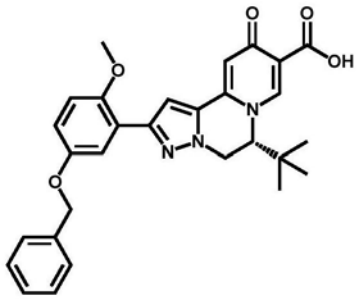
[0624] 实施例35:合成(R)-6-(叔丁基)-10-氧亚基-2-(2,3,6-三甲氧基苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0625] 

[0626] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,3,6-三甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(2,3,6-三甲氧基苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝454.1[M+H]$^+$。

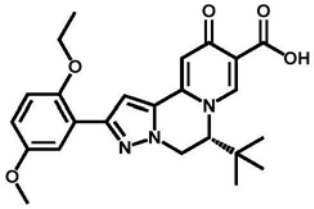
[0627] 实施例36:合成(R)-2-(5-(苄氧基)-2-甲氧基苯基)-6-(叔丁基)-10-氧亚基-5,

6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0628] 

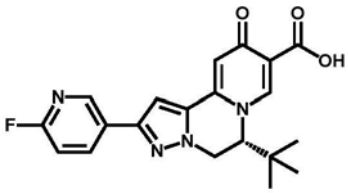
[0629] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(5-(苄氧基)-2-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(5-(苄氧基)-2-甲氧基苯基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝500.1[M+H]$^+$。

[0630] 实施例37:合成(R)-6-(叔丁基)-2-(2-乙氧基-5-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0631] 

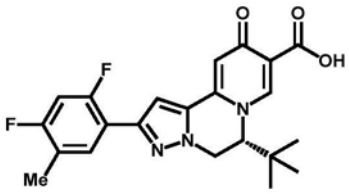
[0632] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-乙氧基-5-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-乙氧基-5-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝438.1[M+H]$^+$。

[0633] 实施例38:合成(R)-6-(叔丁基)-2-(6-氟吡啶-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0634] 

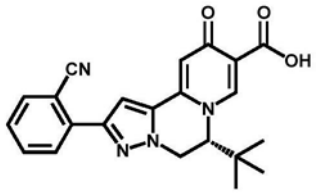
[0635] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(6-氟吡啶-3-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(6-氟吡啶-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝383.1[M+H]$^+$。

[0636] 实施例39:合成(R)-6-(叔丁基)-2-(2,4-二氟-5-甲基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0637] 

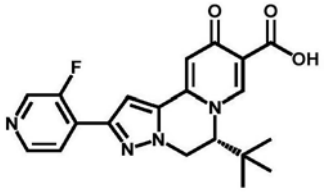
[0638] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,4-二氟-5-甲基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,4-二氟-5-甲基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝414.1[M+H]$^+$。

[0639] 实施例40:合成(R)-6-(叔丁基)-2-(2-氰基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0640] 

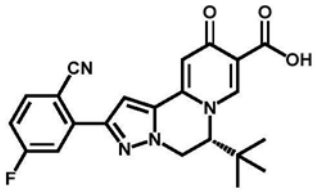
[0641] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氰基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氰基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝389.1[M+H]$^+$。

[0642] 实施例41:合成(R)-6-(叔丁基)-2-(3-氟吡啶-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0643] 

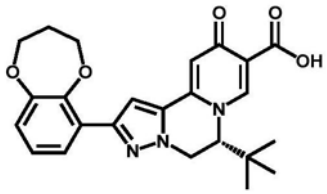
[0644] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3-氟吡啶-4-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(3-氟吡啶-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝383.1[M+H]$^+$。

[0645] 实施例42:合成(R)-6-(叔丁基)-2-(2-氰基-5-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0646] 

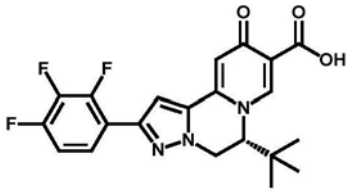
[0647] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氰基-5-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氰基-5-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(0.8mg)。ESI MS m/z＝407.1[M+H]$^+$。

[0648] 实施例43:合成(R)-6-(叔丁基)-2-(3,4-二氢-2H-苯并[b][1,4]二噁庚英-6-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0649] 

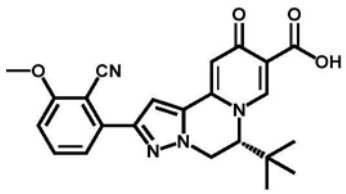
[0650] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3,4-二氢-2H-苯并[b][1,4]二噁庚英-6-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(3,4-二氢-2H-苯并[b][1,4]二噁庚英-6-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝436.1[M+H]$^+$。

[0651] 实施例44:合成(R)-6-(叔丁基)-10-氧亚基-2-(2,3,4-三氟苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0652] 

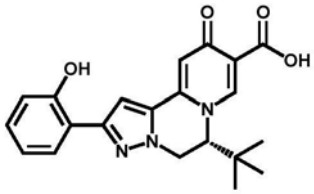
[0653] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,3,4-三氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(2,3,4-三氟苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝418.1[M+H]$^+$。

[0654] 实施例45:合成(R)-6-(叔丁基)-2-(2-氰基-3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0655] 

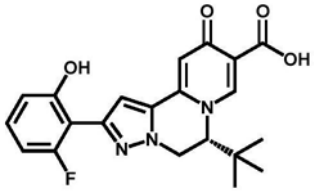
[0656] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氰基-3-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氰基-3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝419.1[M+H]$^+$。

[0657] 实施例46:合成(R)-6-(叔丁基)-2-(2-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0658] 

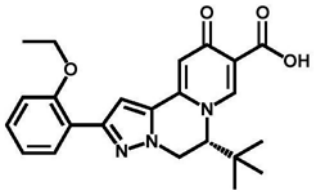
[0659] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-羟基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.1mg)。ESI MS m/z=380.1$[M+H]^+$。

[0660] 实施例47:合成(R)-6-(叔丁基)-2-(2-氟-6-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0661] 

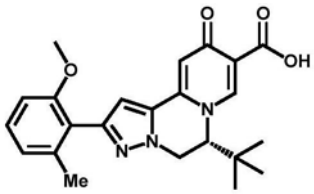
[0662] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氟-6-羟基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氟-6-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.2mg)。ESI MS m/z=398.1$[M+H]^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.29(s,1H),10.59(s,1H),8.59(s,1H),7.28(d,J=3.7Hz,1H),7.24-7.19(m,1H),7.09(s,1H),6.87(d,J=8.4Hz,1H),6.73(ddd,J=11.5,8.3,1.1Hz,1H),4.93(d,J=14.4Hz,1H),4.73(dd,J=14.5,5.2Hz,1H),4.29(d,J=5.0Hz,1H),0.91(s,9H)。

[0663] 实施例48:合成(R)-6-(叔丁基)-2-(2-乙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0664] 

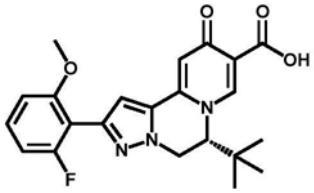
[0665] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-乙氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-乙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z=408.1$[M+H]^+$。^{1}H NMR(400MHz,$CDCl_3$)δ15.50(s,1H),8.54(s,1H),8.02(dd,J=7.7,1.8Hz,1H),7.37-7.29(m,2H),7.06-6.95(m,3H),4.93(d,J=14.4Hz,1H),4.66(dd,J=14.4,5.2Hz,1H),4.22-4.13(m,3H),1.52(t,J=6.9Hz,3H),0.91(s,9H)。

[0666] 实施例49:合成(R)-6-(叔丁基)-2-(2-甲氧基-6-甲基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0667] 

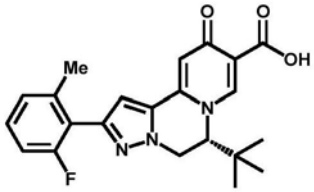
[0668] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-甲氧基-6-甲基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-甲氧基-6-甲基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z=408.1[M+H]$^+$。

[0669] 实施例50:合成(R)-6-(叔丁基)-2-(2-氟-6-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0670] 

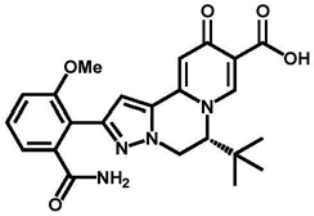
[0671] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氟-6-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氟-6-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z=412.1[M+H]$^+$。

[0672] 实施例51:合成(R)-6-(叔丁基)-2-(2-氟-6-甲基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0673] 

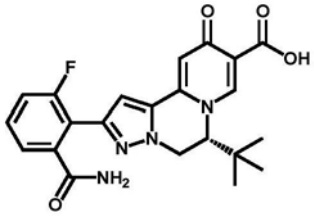
[0674] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氟-6-甲基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氟-6-甲基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z=396.1[M+H]$^+$。

[0675] 实施例52:合成(R)-6-(叔丁基)-2-(2-氨基甲酰基-6-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0676] 

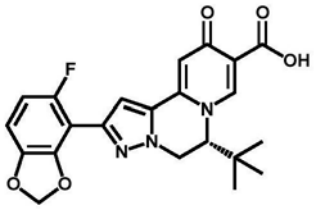
[0677] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氰基-6-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氨基甲酰基-6-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.2mg)。ESI MS m/z=437.1[M+H]$^+$。

[0678] 实施例53:合成(R)-6-(叔丁基)-2-(2-氨基甲酰基-6-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0679] 

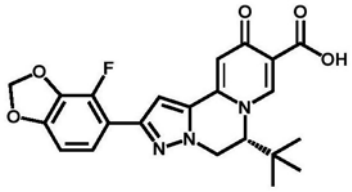
[0680] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氰基-6-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氨基甲酰基-6-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z=425.1[M+H]$^+$。

[0681] 实施例54:合成(R)-6-(叔丁基)-2-(5-氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0682] 

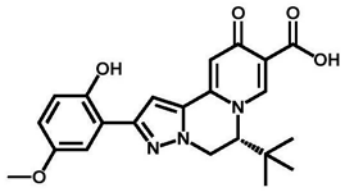
[0683] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(5-氟苯并[d][1,3]二氧杂环戊烯-4-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(5-氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z=426.1[M+H]$^+$。^{1}H NMR (400MHz,$CDCl_3$)δ15.36(s,1H),8.53(s,1H),7.18(d,J=2.3Hz,1H),7.02(s,1H),6.79-6.63(m,2H),6.16(d,J=1.4Hz,1H),6.11(d,J=1.4Hz,1H),5.02(d,J=14.4Hz,1H),4.70(dd,J=14.5,5.2Hz,1H),4.19(d,J=5.1Hz,1H),0.91(s,9H)。

[0684] 实施例55:合成(R)-6-(叔丁基)-2-(4-氟苯并[d][1,3]二氧杂环戊烯-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0685] 

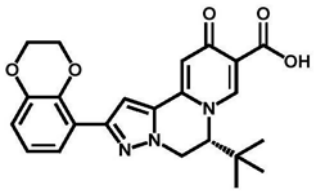
[0686] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(5-氟苯并[d][1,3]二氧杂环戊烯-4-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(4-氟苯并[d][1,3]二氧杂环戊烯-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝426.1[M+H]$^+$。

[0687] 实施例56:合成(R)-6-(叔丁基)-2-(2-羟基-5-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0688] 

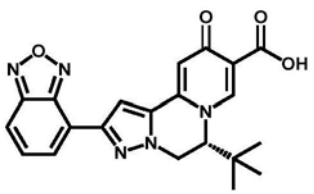
[0689] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-羟基-5-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-羟基-5-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝410.1[M+H]$^+$。

[0690] 实施例57:合成(R)-6-(叔丁基)-2-(2,3-二氢苯并[b][1,4]二噁英-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0691] 

[0692] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,3-二氢苯并[b][1,4]二噁英-5-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,3-二氢苯并[b][1,4]二噁英-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝422.1[M+H]$^+$。

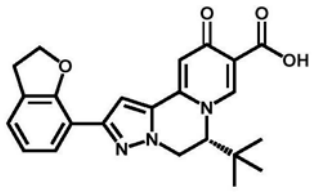
[0693] 实施例58:合成(R)-2-(苯并[c][1,2,5]噁二唑-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0694] 

[0695] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚

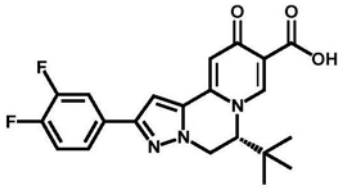
基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用苯并[c][1,2,5]噁二唑-4-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(苯并[c][1,2,5]噁二唑-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝406.1[M+H]$^+$。

[0696] 实施例59:合成(R)-6-(叔丁基)-2-(2,3-二氢苯并呋喃-7-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0697] 

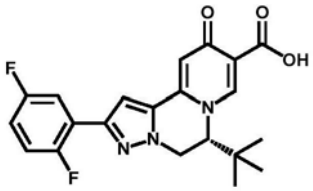
[0698] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,3-二氢苯并呋喃-7-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,3-二氢苯并呋喃-7-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.2mg)。ESI MS m/z＝406.1[M+H]$^+$。

[0699] 实施例60:合成(R)-6-(叔丁基)-2-(3,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0700] 

[0701] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3,4-二氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(3,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.1mg)。ESI MS m/z＝400.1[M+H]$^+$。

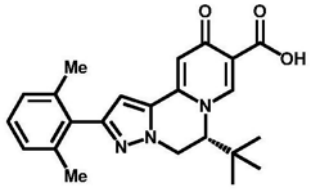
[0702] 实施例61:合成(R)-6-(叔丁基)-2-(2,5-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0703] 

[0704] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,5-二氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,5-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝400.1[M+H]$^+$。

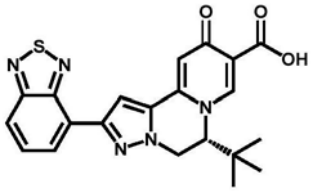
[0705] 实施例62:合成(R)-6-(叔丁基)-2-(2,6-二甲基苯基)-10-氧亚基-5,6-二氢-

10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0706] 

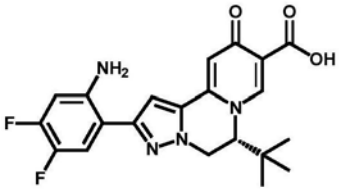
[0707] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2,6-二甲基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2,6-二甲基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.5mg)。ESI MS m/z＝412.1[M+H]$^+$。

[0708] 实施例63:合成(R)-2-(苯并[c][1,2,5]噻二唑-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0709] 

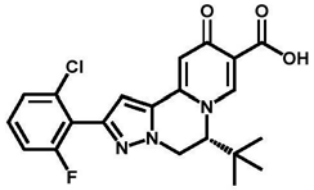
[0710] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用苯并[c][1,2,5]噻二唑-4-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(苯并[c][1,2,5]噻二唑-4-基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝422.1[M+H]$^+$。

[0711] 实施例64:合成(R)-2-(2-氨基-4,5-二氟苯基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0712] 

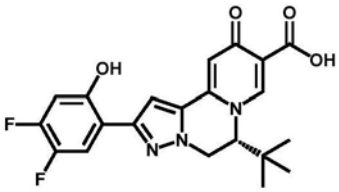
[0713] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氨基-4,5-二氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(2-氨基-4,5-二氟苯基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝415.1[M+H]$^+$。

[0714] 实施例65:合成(R)-6-(叔丁基)-2-(2-氯-6-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0715] 

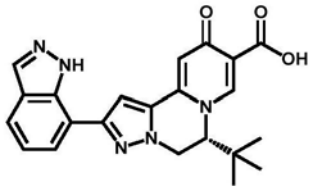
[0716] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-氯-6-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-氯-6-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝416.1[M+H]$^+$。

[0717] 实施例66:合成(R)-6-(叔丁基)-2-(4,5-二氟-2-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0718] 

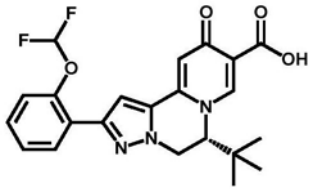
[0719] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(4,5-二氟-2-羟基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(4,5-二氟-2-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.6mg)。ESI MS m/z＝416.1[M+H]$^+$。

[0720] 实施例67:合成(R)-6-(叔丁基)-2-(1H-吲唑-7-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0721] 

[0722] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(1H-吲唑-7-基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(1H-吲唑-7-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝404.1[M+H]$^+$。

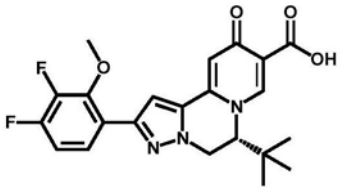
[0723] 实施例68:合成(R)-6-(叔丁基)-2-(2-(二氟甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0724] 

[0725] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚

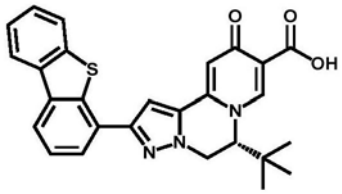
基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(二氟甲氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(二氟甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(2.1mg)。ESI MS m/z＝430.1[M+H]$^+$。

[0726] 实施例69:合成(R)-6-(叔丁基)-2-(3,4-二氟-2-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0727] 

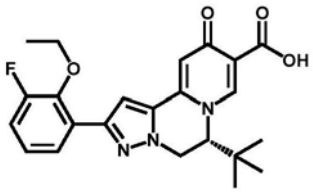
[0728] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(3,4-二氟-2-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(3,4-二氟-2-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.2mg)。ESI MS m/z＝430.1[M+H]$^+$。

[0729] 实施例70:合成(R)-6-(叔丁基)-2-(二苯并[b,d]噻吩-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0730] 

[0731] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用二苯并[b,d]噻吩-4-基硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(二苯并[b,d]噻吩-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1mg)。ESI MS m/z＝470.1[M+H]$^+$。

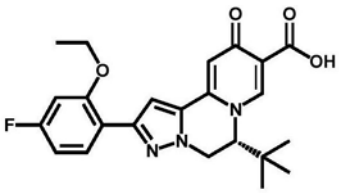
[0732] 实施例71:合成(R)-6-(叔丁基)-2-(2-乙氧基-3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0733] 

[0734] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-乙氧基-3-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-乙氧基-3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝426.1[M+H]$^+$。

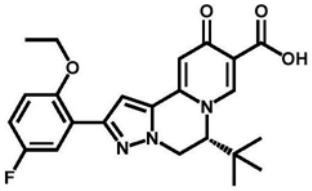
[0735] 实施例72:合成(R)-6-(叔丁基)-2-(2-乙氧基-4-氟苯基)-10-氧亚基-5,6-二氢-

10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0736] 

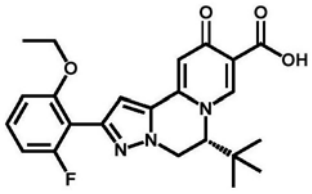
[0737] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-乙氧基-4-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-乙氧基-4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.8mg)。ESI MS m/z＝426.1[M+H]$^+$。

[0738] 实施例73:合成(R)-6-(叔丁基)-2-(2-乙氧基-5-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0739] 

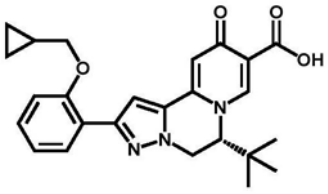
[0740] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-乙氧基-5-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-乙氧基-5-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝426.1[M+H]$^+$。

[0741] 实施例74:合成(R)-6-(叔丁基)-2-(2-乙氧基-6-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0742] 

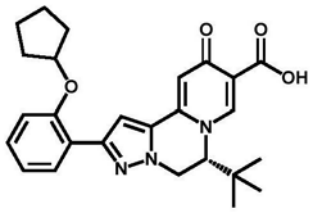
[0743] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-乙氧基-6-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-乙氧基-6-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.4mg)。ESI MS m/z＝426.1[M+H]$^+$。

[0744] 实施例75:合成(R)-6-(叔丁基)-2-(2-(环丙基甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0745] 

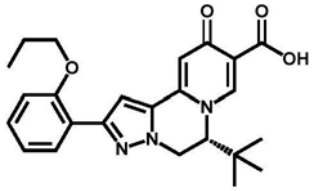
[0746] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(环丙基甲氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(环丙基甲氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝434.1[M+H]$^+$。

[0747] 实施例76:合成(R)-6-(叔丁基)-2-(2-(环戊氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0748] 

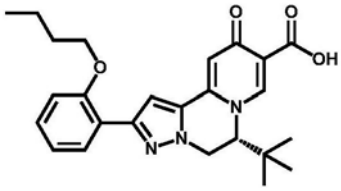
[0749] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(环戊氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(环戊氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.2mg)。ESI MS m/z＝448.1[M+H]$^+$。

[0750] 实施例77:合成(R)-6-(叔丁基)-10-氧亚基-2-(2-丙氧基苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0751] 

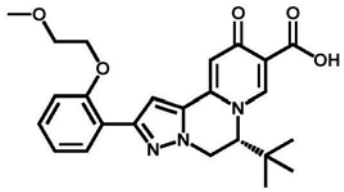
[0752] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-丙氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-10-氧亚基-2-(2-丙氧基苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.6mg)。ESI MS m/z＝422.1[M+H]$^+$。

[0753] 实施例78:合成(R)-2-(2-丁氧基苯基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0754] 

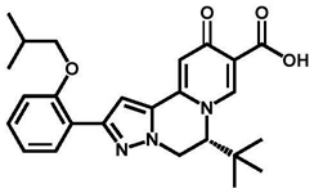
[0755] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-丁氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-2-(2-丁氧基苯基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝436.1[M+H]$^+$。

[0756] 实施例79:合成(R)-6-(叔丁基)-2-(2-(2-甲氧基乙氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0757] 

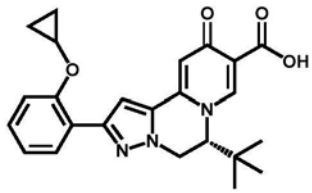
[0758] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(2-甲氧基乙氧基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(2-甲氧基乙氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.1mg)。ESI MS m/z＝438.1[M+H]$^+$。

[0759] 实施例80:合成(R)-6-(叔丁基)-2-(2-异丁氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0760] 

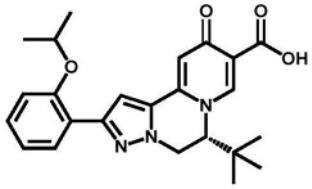
[0761] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-异丁氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-异丁氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z＝436.1[M+H]$^+$。

[0762] 实施例81:合成(R)-6-(叔丁基)-2-(2-环丙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0763] 

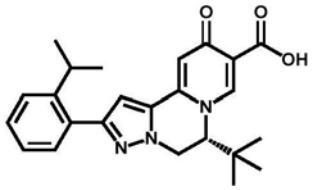
[0764] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-环丙氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-环丙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z＝420.1[M+H]$^+$。

[0765] 实施例82:合成(R)-6-(叔丁基)-2-(2-异丙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0766] 

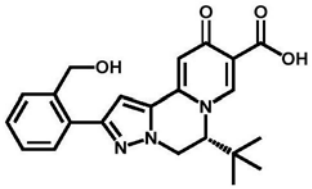
[0767] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-异丙氧基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-异丙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.2mg)。ESI MS m/z=422.1[M+H]$^+$。

[0768] 实施例83:合成(R)-6-(叔丁基)-2-(2-异丙基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0769] 

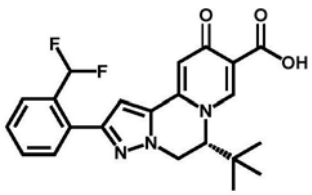
[0770] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-异丙基苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-异丙基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z=406.1[M+H]$^+$。

[0771] 实施例84:合成(R)-6-(叔丁基)-2-(2-(羟基甲基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0772] 

[0773] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(羟基甲基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(羟基甲基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.3mg)。ESI MS m/z=394.1[M+H]$^+$。

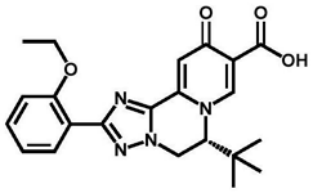
[0774] 实施例85:合成(R)-6-(叔丁基)-2-(2-(二氟甲基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸。

[0775] 

[0776] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚

基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸的程序相同,除了在步骤4中使用(2-(二氟甲基)苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-2-(2-(二氟甲基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,2-c]吡嗪-12-甲酸(1.7mg)。ESI MS m/z=414.1[M+H]$^+$。

[0777] 实施例86:合成(R)-6-(叔丁基)-2-(2-乙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,4]三唑并[5,2-c]吡嗪-12-甲酸。

[0778] 

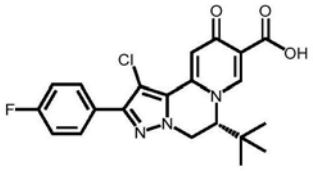
[0779] 步骤1:在烘箱干燥的烧瓶中装入3,5-二溴-1H-1,2,4-三唑(5g,22.04mmol)和THF(100mL)。将反应混合物在冰浴中冷却,并向其中添加氢化钠(582mg,24.24mmol)。在该温度下搅拌20分钟之后,添加在THF(50mL)中呈溶液的(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物(7.39g,26.4mmol)的溶液。然后将反应混合物温热至室温。6h之后,添加MeOH(2mL),然后去除挥发物。将残余物溶解在DCM(100mL)中,然后添加TFA(20mL)。在室温下搅拌14h之后,去除挥发物,并且粗产物无需进一步纯化即用于下一步骤。ESI MS m/z=327.1[M+H]$^+$。

[0780] 步骤2:将来自前一步骤的材料溶解在2:1EtOH:AcOH(25mL)中。向其中添加在EtOH(10mL)中呈溶液的4-氧亚基-4H-吡喃-3-甲酸乙酯(3.09g,18.4mmol)的溶液。将反应混合物加热至回流持续18h,然后使其达到室温。去除挥发物,并将残余物在硅胶上用0-15%MeOH:EtOAc纯化以得到(R)-2-(2-(3,5-二溴-1H-1,2,4-三唑-2-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(1.5g,三个步骤的产率为21%)。ESI MS m/z=477.1[M+H]$^+$。

[0781] 步骤3:在烘箱干燥的小瓶中装入(R)-2-(2-(3,5-二溴-1H-1,2,4-三唑-2-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(530mg,1.11mmol)、$PdBr_2$(59mg,0.223mmol)、KOAc(328mg,3.34mmol)以及DMF(25mL)。将反应混合物在90℃下搅拌14h。然后,去除DMF,并将残余物在硅胶上用0-15%MeOH:EtOAc纯化以得到(R)-2-溴-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,4]三唑并[5,2-c]吡嗪-12-甲酸乙酯(6mg,1%产率)。ESI MS m/z=396.1[M+H]$^+$。

[0782] 步骤4:在烘箱干燥的小瓶中装入(R)-2-溴-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,4]三唑并[5,2-c]吡嗪-12-甲酸乙酯(6mg,0.015mmol)、(2-乙氧基苯基)硼酸(4mg,0.023mmol)、Cs_2CO_3(15mg,0.046mmol)以及Pd-XPhos-G3(1.2mg,0.002mmol)。用氮气吹扫小瓶,然后添加1,4-二噁烷(2mL)和水(1mL)。将反应混合物在100℃下加热持续16h,然后使其达到室温。将反应混合物用DCM(5mL)稀释并将pH用1M的HCl水溶液调节至3。用DCM(3x5 mL)萃取产物,并将合并的有机层浓缩。将残余物通过RP-HPLC纯化以得到(R)-6-(叔丁基)-2-(2-乙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,4]三唑并[5,2-c]吡嗪-12-甲酸(1.7mg,29%产率)。ESI MS m/z=409.1[M+H]$^+$。

[0783] 实施例87:合成(R)-6-(叔丁基)-1-氯-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0784] 

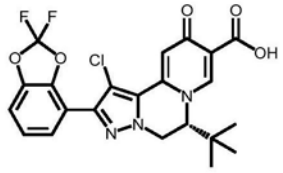
[0785] 步骤1:在0℃下向4-氯-1H-吡唑(80.0g)和NaOH(125.5g)在水(1.5L)中的溶液中逐滴添加Br_2(100.0mL)。在添加之后,将混合物在室温下搅拌过夜,然后用2N的HCl水溶液使其呈酸性。将固体过滤并用水(500mL x 3)洗涤。将滤饼用PE/EA(10:1)研磨若干次并过滤。将白色固体在真空中干燥,以得到3,5-二溴-4-氯-1H-吡唑(101g,50%产率)。^{1}H NMR(400MHz,DMSO-d_6)δ14.14(s,1H)。^{13}C NMR(100MHz,DMSO-d_6)δ119.70,110.95。

[0786] 步骤2:在氮气下将3,5-二溴-4-氯-1H-吡唑(5.0g)在THF(100mL)中的溶液冷却至0℃。分批添加60wt%的氢化钠(0.845g)。使混合物在0℃下搅拌直到停止冒泡。在0℃下分批添加(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物(6.44g)。将混合物搅拌5min,然后使其达到室温。将反应混合物搅拌额外的30min,然后向空气开放并用少量的甲醇淬灭。去除挥发物并将残余物溶解在DCM(100mL)中。然后,添加三氟乙酸(37mL)并将所得溶液搅拌15min。去除挥发物并将残余物溶解在乙醇(48mL)和乙酸(24mL)中。然后,4-氧亚基-4H-吡喃-3-甲酸乙酯(4.84g)作为在乙醇(24mL)中的溶液添加。将混合物加热至回流持续5h。去除挥发物,并将产物在硅胶上纯化(MeOH:EtOAc 0-15%)以得到(R)-1-(1-(3,5-二溴-4-氯-1H-吡唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(2100mg,21%产率)。

[0787] 步骤3:在氮气下在微波小瓶中装入(R)-1-(1-(3,5-二溴-4-氯-1H-吡唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(500mg)、新戊酸铯(690mg)、溴化钯(II)(250mg)以及DMF(20mL)。使氮气通过所得溶液鼓泡10min。将所得溶液在微波中在120℃下加热60min。将所得溶液过滤、浓缩并在硅胶上纯化(MeOH:EtOAc 0-15%)以得到(R)-2-溴-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(313mg,74%产率)。

[0788] 步骤4:将2-(4-氟苯基)-4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷(16mg)、(R)-2-溴-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(27mg)、碳酸铯(61mg)以及Pd(PPh_3)$_4$(7mg)在1,4-二噁烷(1.4mL)和水(0.7mL)中的溶液在100℃下在搅拌下在密封小瓶中加热16h。冷却至室温之后,添加二氯甲烷和1N HCl。将反应混合物用二氯甲烷萃取并将有机层浓缩。将残余物通过RPHPLC纯化以得到(R)-6-(叔丁基)-1-氯-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4.4mg,17%产率)。ESI MS m/z=416.1$[M+H]^+$。

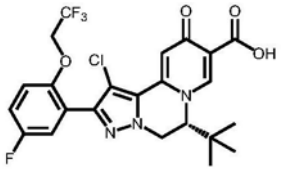
[0789] 实施例88:合成(R)-6-(叔丁基)-1-氯-2-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0790] 

[0791] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-氯-2-(4-氟苯基)-10-

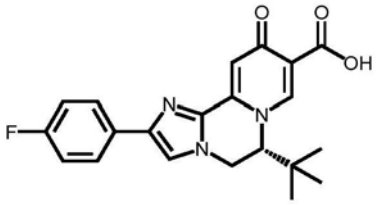
氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例87)的程序相同,除了在步骤4中使用2-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷代替2-(4-氟苯基)-4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷之外,以得到(R)-6-(叔丁基)-1-氯-2-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2.2mg)。ESI MS m/z＝478.1[M+H]$^+$。

[0792] 实施例89:合成(R)-6-(叔丁基)-1-氯-2-(5-氟-2-(2,2,2-三氟乙氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0793] 

[0794] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-氯-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例87)的程序相同,除了在步骤4中使用2-(5-氟-2-(2,2,2-三氟乙氧基)苯基)-4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷代替2-(4-氟苯基)-4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷之外,以得到(R)-6-(叔丁基)-1-氯-2-(5-氟-2-(2,2,2-三氟乙氧基)苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1.1mg)。ESI MS m/z＝514.1[M+H]$^+$。

[0795] 实施例90:合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,2-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0796] 

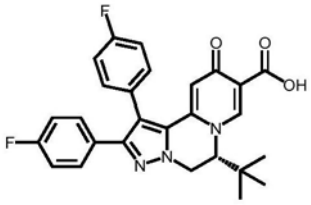
[0797] 步骤1:在氮气下将2,4-二溴-1H-咪唑(5.0g)在THF(100mL)中的溶液冷却至0℃。分批添加60wt%的氢化钠(0.975g)。使混合物在0℃下搅拌直到停止冒泡。在0℃下分批添加(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物(7.42g)。将混合物搅拌5min,然后使其达到室温。将反应混合物搅拌额外的30min,然后向空气开放并用少量的甲醇淬灭。去除挥发物并将残余物溶解在DCM(100mL)中。然后,添加三氟乙酸(43mL)并将所得溶液搅拌15min。去除挥发物并将残余物溶解在乙醇(55mL)和乙酸(28mL)中。然后,4-氧亚基-4H-吡喃-3-甲酸乙酯(5.6g)作为在乙醇(55mL)中的溶液添加。将混合物加热至回流持续5h。去除挥发物,并将产物在硅胶上纯化(MeOH:EtOAc 0-15%)以得到(R)-1-(1-(3,5-二溴-4-氯-1H-吡唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(2g,19%产率)。

[0798] 步骤2:在氮气下在微波小瓶中装入(R)-1-(1-(2,4-二溴-1H-咪唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(60mg)、新戊酸铯(89mg)、PCy_3-Pd G4(9mg)以及DMF(5mL)。使氮气通过所得溶液鼓泡10min。将所得溶液在微波中在130℃下加热10min。将所得溶液过滤、浓缩并在硅胶上纯化(MeOH:EtOAc 0-15%)以得到(R)-2-溴-6-

(叔丁基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,2-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(10mg,16%产率)。

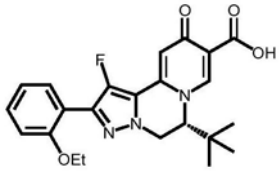
[0799] 步骤3:将2-(4-氟苯基)-4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷(15mg)、(R)-2-溴-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,2-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(22mg)、碳酸铯(55mg)以及XPhos-Pd G3(5mg)在1,4-二噁烷(1.4mL)和水(0.7mL)中的溶液在100℃下在搅拌下在密封小瓶中加热16h。冷却至室温之后,添加二氯甲烷和1N HCl。将反应混合物用二氯甲烷萃取并将有机层浓缩。将残余物通过RPHPLC纯化以得到(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,2-a]吡啶并[2,1-c]吡嗪-9-甲酸(7.4mg,35%产率)。ESI MS m/z=382.1[M+H]$^+$。

[0800] 实施例91:合成(R)-6-(叔丁基)-1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0801] 

[0802] 将(4-氟苯基)硼酸(41mg)、(R)-2-溴-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(27mg)、碳酸铯(42mg)以及XPhos-Pd G3(2mg)在1,4-二噁烷(1.4mL)和水(0.7mL)中的溶液在100℃下在搅拌下在密封小瓶中加热16h。冷却至室温之后,添加二氯甲烷和1N HCl。将反应混合物用二氯甲烷萃取并将有机层浓缩。将残余物通过RPHPLC纯化以得到(R)-6-(叔丁基)-1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3.9mg,8%产率)。ESI MS m/z=476.1[M+H]$^+$。

[0803] 实施例92:合成(R)-6-(叔丁基)-2-(2-乙氧基苯基)-1-氟-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0804] 

[0805] 步骤1:将3,5-二溴-1H-吡唑(5.0g)和选择性氟试剂(23.5g)在MeCN(110mL)中的溶液加热至100℃持续16h。冷却至室温之后,将反应混合物用乙酸乙酯稀释,并用水洗涤。将有机层干燥、过滤并浓缩以得到3,5-二溴-4-氟-1H-吡唑(5.4g,99%产率),其无需任何额外纯化直接使用。

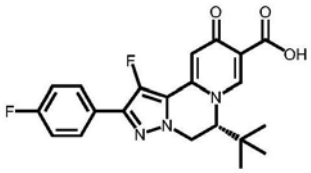
[0806] 步骤2:在氮气下将3,5-二溴-4-氟-1H-吡唑(540mg)在THF(11mL)中的溶液冷却至0℃。添加60wt%的氢化钠(97mg)。使混合物在0℃下搅拌直到停止冒泡。在0℃下分批添加(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物(740mg)。将混合物搅拌5min,然后使其达到室温。将反应混合物搅拌额外的30min,然后向空气开放并用少量的甲醇淬灭。去除挥发物并将残余物溶解在DCM(10mL)中。然后,添加三氟乙酸(4mL)并将所得溶液搅拌15min。去除挥发物并将残余物溶解在乙醇(5mL)和乙酸(3mL)中。然后,4-氧亚基-

4H-吡喃-3-甲酸乙酯(559mg)作为在乙醇(5mL)中的溶液添加。将混合物加热至回流持续5h。去除挥发物,并将产物在硅胶上纯化(MeOH:EtOAc 0-15%)以得到(R)-1-(1-(3,5-二溴-4-氟-1H-吡唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(183mg,17%产率)。

[0807] 步骤3:在氮气下在微波小瓶中装入(R)-1-(1-(3,5-二溴-4-氟-1H-吡唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(30mg)、新戊酸铯(40mg)、PCy_3-Pd G4(3mg)以及DMF(2mL)。使氮气通过所得溶液鼓泡10min。将所得溶液在微波中在120℃下加热30min。将所得溶液过滤、浓缩并在硅胶上纯化(MeOH:EtOAc 0-15%)以得到(R)-2-溴-6-(叔丁基)-1-氟-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(5mg,22%产率)。

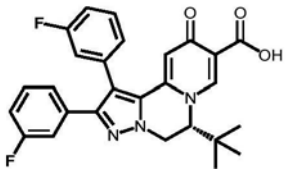
[0808] 步骤4:将(2-乙氧基苯基)硼酸(24mg)、(R)-2-溴-6-(叔丁基)-1-氟-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(50mg)、碳酸铯(120mg)以及$Pd(Ph_3P)_4$(14mg)在1,4-二噁烷(3mL)和水(1.5mL)中的溶液在100℃下在搅拌下在密封小瓶中加热16h。冷却至室温之后,添加二氯甲烷和1N HCl。将反应混合物用二氯甲烷萃取并将有机层浓缩。将残余物通过RPHPLC纯化以得到(R)-6-(叔丁基)-2-(2-乙氧基苯基)-1-氟-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3.2mg,6%产率)。ESI MS m/z=426.1$[M+H]^+$。

[0809] 实施例93:合成(R)-6-(叔丁基)-1-氟-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0810] 

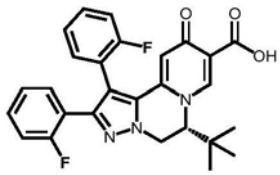
[0811] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(2-乙氧基苯基)-1-氟-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例92)的程序相同,除了在步骤3中使用(4-氟苯基)硼酸代替(2-乙氧基苯基)硼酸之外,以得到(R)-6-(叔丁基)-1-氟-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(11mg)。ESI MS m/z=400.1$[M+H]^+$。

[0812] 实施例94:合成(R)-6-(叔丁基)-1,2-双(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0813] 

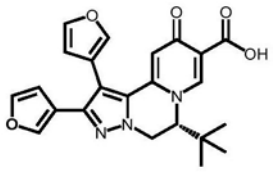
[0814] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例91)的程序相同,除了使用(3-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1,2-双(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1.5mg)。ESI MS m/z=476.1$[M+H]^+$。

[0815] 实施例95:合成(R)-6-(叔丁基)-1,2-双(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0816] 

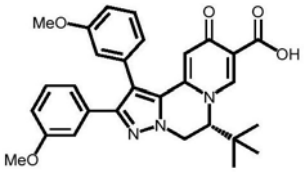
[0817] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例91)的程序相同,除了使用(2-氟苯基)硼酸代替(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1,2-双(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2.1mg)。ESI MS m/z=476.1[M+H]$^+$。

[0818] 实施例96:合成(R)-6-(叔丁基)-1,2-二(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0819] 

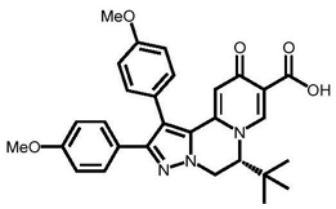
[0820] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例91)的程序相同,除了使用2-(呋喃-3-基)-4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷代替(4-氟苯基)硼酸(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1,2-二(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1.2mg)。ESI MS m/z=420.1[M+H]$^+$。

[0821] 实施例97:合成(R)-6-(叔丁基)-1,2-双(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0822] 

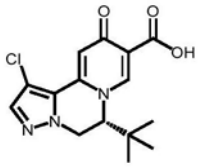
[0823] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例91)的程序相同,除了使用(3-甲氧基苯基)硼酸代替(4-氟苯基)硼酸(4-氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1,2-双(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2.1mg)。ESI MS m/z=500.1[M+H]$^+$。

[0824] 实施例98:合成(R)-6-(叔丁基)-1,2-双(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0825] 

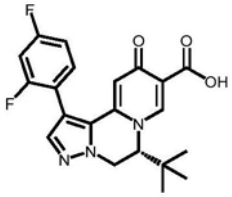
[0826] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例91)的程序相同，除了使用(4-甲氧基苯基)硼酸代替(4-氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1,2-双(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(22mg)。ESI MS m/z＝500.1[M+H]$^+$。

[0827] 实施例99：合成(R)-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0828] 

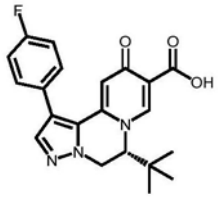
[0829] 步骤1：将(R)-2-溴-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(50mg)、碳酸铯(120mg)以及Pd(PPh$_3$)$_4$(15mg)在1,4-二噁烷(3mL)和水(1mL)中的溶液在80℃下在搅拌下在密封小瓶中加热8h。冷却至室温之后，添加二氯甲烷和1N HCl。将反应混合物用二氯甲烷萃取并将有机层浓缩。将残余物通过RPHPLC纯化以得到(R)-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(12mg)。ESI MS m/z＝322.1[M+H]$^+$。

[0830] 实施例100：合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0831] 

[0832] 步骤1：将(R)-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(50mg)、(2,4-二氟苯基)硼酸(62mg)、碳酸铯(120mg)以及Pd-XPhos-G3(12mg)在DMF(3mL)和水(1mL)中的溶液在120℃下在搅拌下在密封小瓶中加热11h。冷却至室温之后，添加1N HCl。将反应混合物通过相分离器过滤并浓缩。将残余物通过RPHPLC纯化以得到(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝400.1[M+H]$^+$。

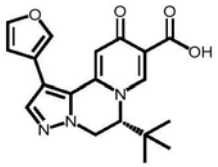
[0833] 实施例101：合成(R)-6-(叔丁基)-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0834] 

[0835] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(4-氟苯基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(4-氟

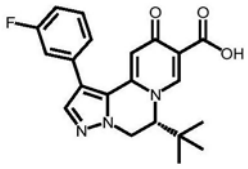
苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝382.1[M+H]$^+$。

[0836] 实施例102:合成(R)-6-(叔丁基)-1-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0837] 

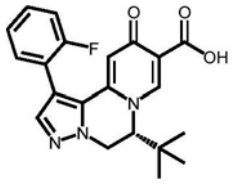
[0838] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同,除了使用3-呋喃基-硼酸代替(2,4-二氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z＝354.1[M+H]$^+$。

[0839] 实施例103:合成(R)-6-(叔丁基)-1-(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0840] 

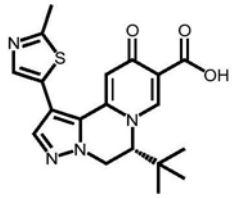
[0841] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同,除了使用(3-氟苯基)硼酸代替(2,4-二氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1-(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z＝382.1[M+H]$^+$。

[0842] 实施例104:合成(R)-6-(叔丁基)-1-(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0843] 

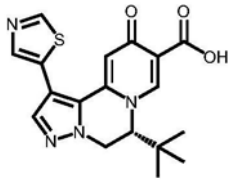
[0844] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同,除了使用(2-氟苯基)硼酸代替(2,4-二氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1-(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝382.1[M+H]$^+$。

[0845] 实施例105:合成(R)-6-(叔丁基)-1-(2-甲基噻唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0846] 

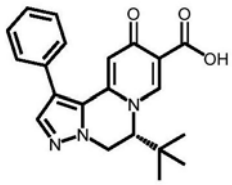
[0847] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(2-甲基噻唑-5-基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(2-甲基噻唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝385.1[M+H]$^+$。

[0848] 实施例106：合成(R)-6-(叔丁基)-10-氧亚基-1-(噻唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0849] 

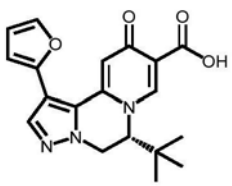
[0850] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用噻唑-5-基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(噻唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝371.1[M+H]$^+$。

[0851] 实施例107：合成(R)-6-(叔丁基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0852] 

[0853] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用苯基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝364.1[M+H]$^+$。

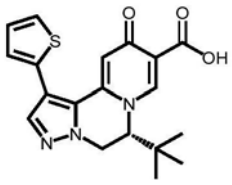
[0854] 实施例108：合成(R)-6-(叔丁基)-1-(呋喃-2-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0855] 

[0856] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧

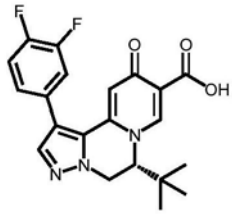
亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用呋喃-2-基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(呋喃-2-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝354.1[M+H]$^+$。

[0857] 实施例109:合成(R)-6-(叔丁基)-10-氧亚基-1-(噻吩-2-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0858] 

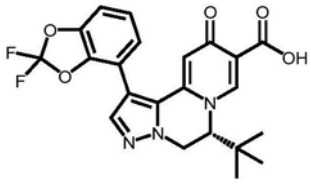
[0859] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用噻吩-2-基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(噻吩-2-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(8mg)。ESI MS m/z＝370.1[M+H]$^+$。

[0860] 实施例110:合成(R)-6-(叔丁基)-1-(3,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0861] 

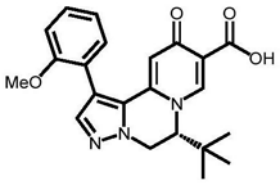
[0862] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(3,4-二氟苯基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(3,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝400.1[M+H]$^+$。

[0863] 实施例111:合成(R)-6-(叔丁基)-1-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0864] 

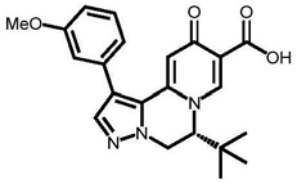
[0865] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(6mg)。ESI MS m/z＝444.1[M+H]$^+$。

[0866] 实施例112:合成(R)-6-(叔丁基)-1-(2-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0867] 

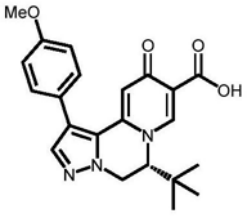
[0868] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同,除了使用(2-甲氧基苯基)硼酸代替(2,4-二氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1-(2-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(7mg)。ESI MS m/z=394.1[M+H]$^+$。

[0869] 实施例113:合成(R)-6-(叔丁基)-1-(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0870] 

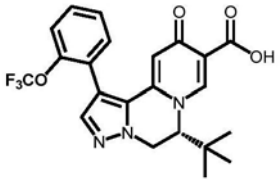
[0871] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同,除了使用(3-甲氧基苯基)硼酸代替(2,4-二氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1-(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(10mg)。ESI MS m/z=394.1[M+H]$^+$。

[0872] 实施例114:合成(R)-6-(叔丁基)-1-(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0873] 

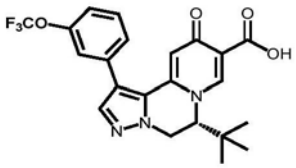
[0874] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同,除了使用(4-甲氧基苯基)硼酸代替(2,4-二氟苯基)硼酸之外,以得到(R)-6-(叔丁基)-1-(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(11mg)。ESI MS m/z=394.1[M+H]$^+$。

[0875] 实施例115:合成(R)-6-(叔丁基)-10-氧亚基-1-(2-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0876] 

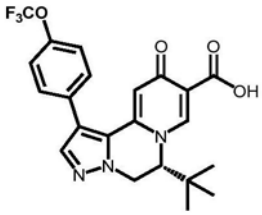
[0877] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(2-(三氟甲氧基)苯基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(2-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝448.1[M+H]$^+$。

[0878] 实施例116:合成(R)-6-(叔丁基)-10-氧亚基-1-(3-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0879] 

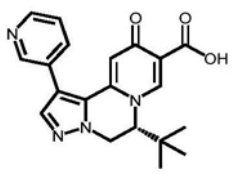
[0880] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(3-(三氟甲氧基)苯基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(3-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(12mg)。ESI MS m/z＝448.1[M+H]$^+$。

[0881] 实施例117:合成(R)-6-(叔丁基)-10-氧亚基-1-(4-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0882] 

[0883] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(4-(三氟甲氧基)苯基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(4-(三氟甲氧基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z＝448.1[M+H]$^+$。

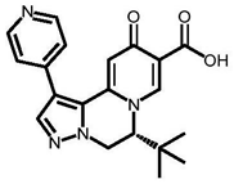
[0884] 实施例118:合成(R)-6-(叔丁基)-10-氧亚基-1-(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0885] 

[0886] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧

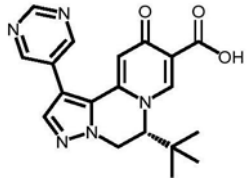
亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用吡啶-3-基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝365.1[M+H]$^+$。

[0887] 实施例119:合成(R)-6-(叔丁基)-10-氧亚基-1-(吡啶-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0888] 

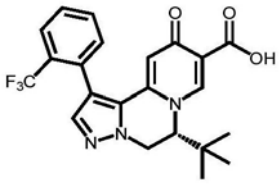
[0889] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用吡啶-4-基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(吡啶-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝365.1[M+H]$^+$。

[0890] 实施例120:合成(R)-6-(叔丁基)-10-氧亚基-1-(嘧啶-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0891] 

[0892] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用嘧啶-5-基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(嘧啶-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝366.1[M+H]$^+$。

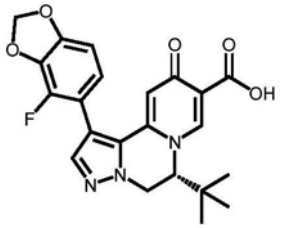
[0893] 实施例121:合成(R)-6-(叔丁基)-10-氧亚基-1-(2-(三氟甲基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0894] 

[0895] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(2-(三氟甲基)苯基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(2-(三氟甲基)苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝432.1[M+H]$^+$。

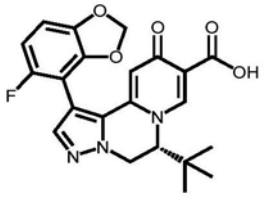
[0896] 实施例122:合成(R)-6-(叔丁基)-1-(4-氟苯并[d][1,3]二氧杂环戊烯-5-基)-

10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0897] 

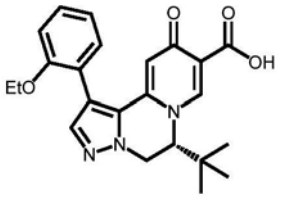
[0898] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(4-氟苯并[d][1,3]二氧杂环戊烯-5-基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(4-氟苯并[d][1,3]二氧杂环戊烯-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(10mg)。ESI MS m/z＝426.1[M+H]$^+$。

[0899] 实施例123：合成(R)-6-(叔丁基)-1-(5-氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0900] 

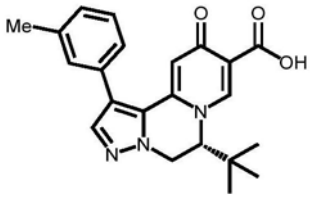
[0901] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(5-氟苯并[d][1,3]二氧杂环戊烯-4-基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(5-氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(13mg)。ESI MS m/z＝426.1[M+H]$^+$。

[0902] 实施例124：合成(R)-6-(叔丁基)-1-(2-乙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0903] 

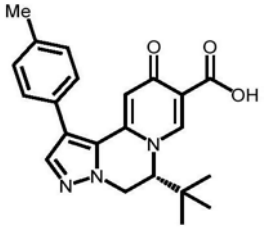
[0904] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用(2-乙氧基苯基)硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-1-(2-乙氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z＝408.1[M+H]$^+$。

[0905] 实施例125：合成(R)-6-(叔丁基)-10-氧亚基-1-(间甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0906] 

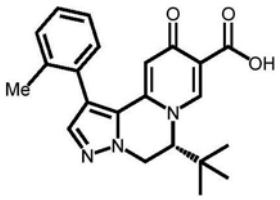
[0907] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用间甲苯基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(间甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(7mg)。ESI MS m/z＝378.1[M+H]$^+$。

[0908] 实施例126：合成(R)-6-(叔丁基)-10-氧亚基-1-(对甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0909] 

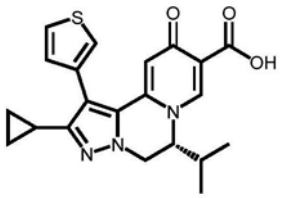
[0910] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用对甲苯基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(对甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z＝378.1[M+H]$^+$。

[0911] 实施例127：合成(R)-6-(叔丁基)-10-氧亚基-1-(邻甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0912] 

[0913] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-1-(2,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例100)的程序相同，除了使用邻甲苯基硼酸代替(2,4-二氟苯基)硼酸之外，以得到(R)-6-(叔丁基)-10-氧亚基-1-(邻甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(8mg)。ESI MS m/z＝378.1[M+H]$^+$。

[0914] 实施例128：合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0915] 

[0916] 步骤1:在0℃下向3,5-二溴-4-氯-1H-吡唑(48g,184.62mmol,1.00当量)在THF中的搅拌溶液中分批添加NaH(14.8g,369.24mmol,2.00当量,60%)。在0℃下向上述混合物中添加(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物(48.9g,184.62mmol,1.00当量)。将所得混合物在室温下搅拌额外的2h。将反应在室温下用水淬灭。将所得混合物用EtOAc(3x1L)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,将滤液在减压下浓缩以得到N-[(2R)-1-(3,5-二溴-4-氯吡唑-1-基)-3-甲基丁-2-基]氨基甲酸叔丁酯(85g,粗品),为黄色固体。

[0917] 步骤2:在-40℃下在氮气气氛下,向N-[(2R)-1-(3,5-二溴-4-氯吡唑-1-基)-3-甲基丁-2-基]氨基甲酸叔丁酯(85g,188.34mmol,1.00当量)在THF中的搅拌溶液中逐滴添加氯(异丙基)镁(565mL,565mmol,3.00当量,1M)。在-40℃下向上述混合物中逐滴添加DMF(137.5g,1883.4mmol,10.00当量)。将所得混合物在-40℃下搅拌额外的1h。将反应在室温下用饱和NH_4Cl(水溶液)淬灭。将所得混合物用EtOAc(3x1L)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,将滤液在减压下浓缩以得到(R)-(1-(5-溴-4-氯-3-甲酰基-1H-吡唑-1-基)-3-甲基丁-2-基)氨基甲酸叔丁酯(80g,粗品),为黄色油。

[0918] 步骤3:将N-[(2R)-1-(5-溴-4-氯-3-甲酰基吡唑-1-基)-3-甲基丁-2-基]氨基甲酸叔丁酯(80g,粗品)在TFA(100.00mL)和DCM(100.00mL)中的溶液在室温下搅拌过夜。将混合物浓缩并通过硅胶纯化(PE/EtOAc=10/1)以得到(R)-2-溴-3-氯-6-异丙基-6,7-二氢吡唑并[1,5-a]吡嗪(20g),为黄色油。

[0919] 步骤4:将(R)-2-溴-3-氯-6-异丙基-6,7-二氢吡唑并[1,5-a]吡嗪(5.5g,19.78mmol,1.00当量)和(Z)-2-(乙氧基亚甲基)-3-氧亚基丁酸乙酯(11.0g,59.35mmol,3.00当量)在EtOH中的溶液在回流下搅拌过夜。将混合物浓缩并通过RPHPLC纯化以得到(6R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6,11,11a-四氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(3.5g,43%),为黄色油。

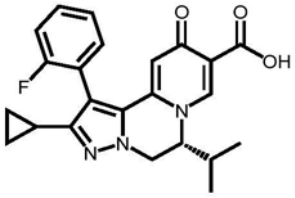
[0920] 步骤5:将(6R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6,11,11a-四氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(3.5g,8.39mmol,1.00当量)以及对氯醌(4.10g)在DME中的溶液在70℃下搅拌3h。将混合物浓缩并通过RPHPLC纯化以得到(R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(2.6g,74%),为黄色油。

[0921] 步骤6:将(R)-2-溴-1-氯-6-异丙基-10-氧亚基-6,10-二氢-5H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(500mg,1.20mmol,1.00当量)、环丙基硼酸(258mg,3.00mmol,2.5当量)、$Pd(PPh_3)_4$(139mg,0.12mmol,0.1当量)以及Cs_2CO_3(782mg,2.40mmol,2.00当量)在二噁烷(10ml)和H_2O(2ml)中的混合物在氮气气氛下在100℃下搅拌过夜。将混合物用H_2O(10ml)稀释,用EtOAc(3x20ml)萃取。将有机层通过盐水洗涤,用Na_2SO_4干燥并在减压下浓缩。将残余物通过RPHPLC纯化(H_2O/MeCN,0%至100%,20min)以得到(R)-1-氯-2-环丙基-6-异丙基-10-氧亚基-6,10-二氢-5H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸

(350mg,88.3%),为棕色固体。

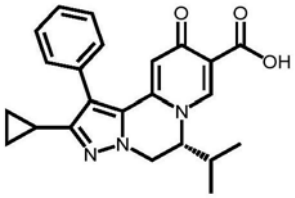
[0922] 步骤7:向(R)-1-氯-2-环丙基-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(50.00mg,0.144mmol,1.00当量)和噻吩-3-基硼酸(91.97mg,0.719mmol,5.00当量)在DMF(2.00mL)和H_2O(0.20mL)中的溶液中添加Cs_2CO_3(140.52mg,0.431mmol,3.00当量)以及Xphos Pd G3(24.34mg,0.029mmol,0.20当量)。在氮气气氛下在120℃下搅拌过夜之后,将混合物用H_2O(10ml)稀释,用EtOAc(3x20ml)萃取。将有机层通过盐水洗涤,用Na2SO4干燥并在减压下浓缩。将粗产物通过RPHPLC纯化以得到(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(21mg,37%),为黄色固体。ESI MS m/z=396.1$[M+H]^+$。

[0923] 实施例129:合成(R)-2-环丙基-1-(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0924] 

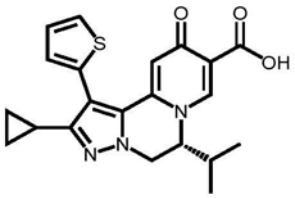
[0925] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(2-氟苯基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z=408.1$[M+H]^+$。

[0926] 实施例130:合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0927] 

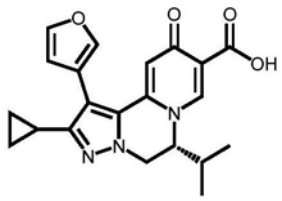
[0928] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用苯基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(22mg)。ESI MS m/z=390.1$[M+H]^+$。

[0929] 实施例131:合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-2-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0930] 

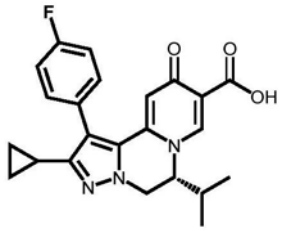
[0931] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用噻吩-2-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-2-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(12mg)。ESI MS m/z＝396.1[M+H]$^+$。

[0932] 实施例132:合成(R)-2-环丙基-1-(呋喃-3-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0933] 

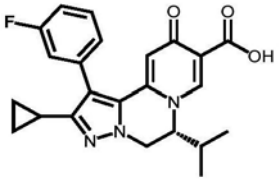
[0934] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用呋喃-3-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(呋喃-3-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝380.1[M+H]$^+$。

[0935] 实施例133:合成(R)-2-环丙基-1-(4-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0936] 

[0937] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(4-氟苯基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(4-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(16mg)。ESI MS m/z＝408.1[M+H]$^+$。

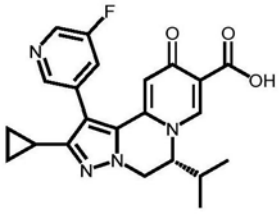
[0938] 实施例134:合成(R)-2-环丙基-1-(3-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0939] 

[0940] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(3-氟苯基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(3-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸

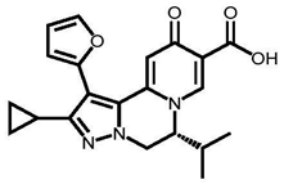
(5mg)。ESI MS m/z＝408.1[M+H]$^+$。

[0941] 实施例135:合成(R)-2-环丙基-1-(5-氟吡啶-3-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0942] 

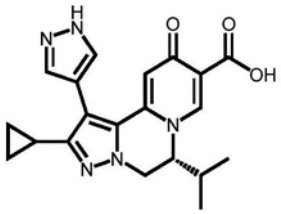
[0943] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(5-氟吡啶-3-基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(5-氟吡啶-3-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝409.1[M+H]$^+$。

[0944] 实施例136:合成(R)-2-环丙基-1-(呋喃-2-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0945] 

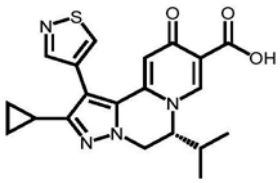
[0946] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用呋喃-2-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(呋喃-2-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(7mg)。ESI MS m/z＝380.1[M+H]$^+$。

[0947] 实施例137:合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(1H-吡唑-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0948] 

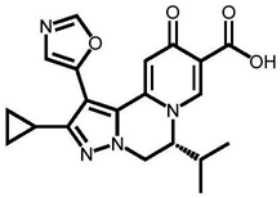
[0949] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(1H-吡唑-4-基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-10-氧亚基-1-(1H-吡唑-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(13mg)。ESI MS m/z＝380.1[M+H]$^+$。

[0950] 实施例138:合成(R)-2-环丙基-6-异丙基-1-(异噻唑-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0951] 

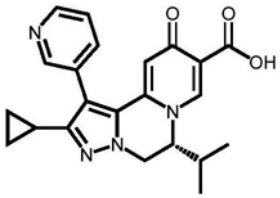
[0952] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用异噻唑-4-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-1-(异噻唑-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝397.1[M+H]$^+$。

[0953] 实施例139:合成(R)-2-环丙基-6-异丙基-1-(噁唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0954] 

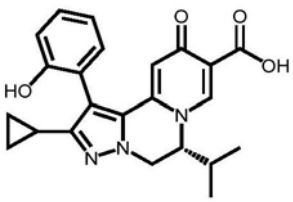
[0955] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用噁唑-5-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-1-(噁唑-5-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝381.1[M+H]$^+$。

[0956] 实施例140:合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0957] 

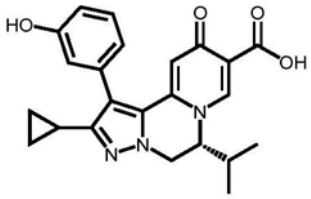
[0958] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用吡啶-3-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-10-氧亚基-1-(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(8mg)。ESI MS m/z＝391.1[M+H]$^+$。

[0959] 实施例141:合成(R)-2-环丙基-1-(2-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0960] 

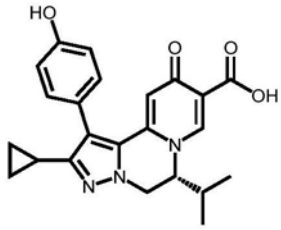
[0961] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(2-羟基苯基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(2-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(14mg)。ESI MS m/z＝406.1[M+H]$^+$。

[0962] 实施例142:合成(R)-2-环丙基-1-(3-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0963] 

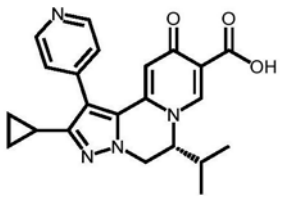
[0964] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(3-羟基苯基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(3-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝406.1[M+H]$^+$。

[0965] 实施例143:合成(R)-2-环丙基-1-(4-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0966] 

[0967] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用(4-羟基苯基)硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-1-(4-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝406.1[M+H]$^+$。

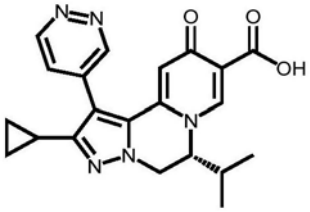
[0968] 实施例144:合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(吡啶-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0969] 

[0970] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用吡啶-4-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-10-氧亚基-1-(吡啶-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸

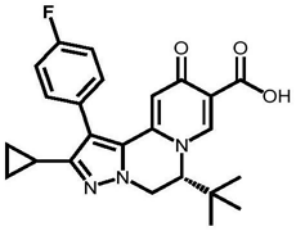
(17mg)。ESI MS m/z＝391.1[M+H]$^+$。

[0971] 实施例145:合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(哒嗪-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0972] 

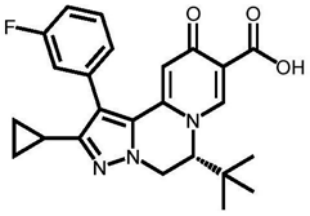
[0973] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了使用哒嗪-4-基硼酸代替噻吩-3-基硼酸之外,以得到(R)-2-环丙基-6-异丙基-10-氧亚基-1-(哒嗪-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝392.1[M+H]$^+$。

[0974] 实施例146:合成(R)-6-(叔丁基)-2-环丙基-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0975] 

[0976] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(4-氟苯基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(9mg)。ESI MS m/z＝422.1[M+H]$^+$。

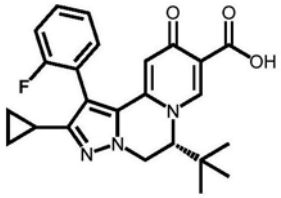
[0977] 实施例147:合成(R)-6-(叔丁基)-2-环丙基-1-(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0978] 

[0979] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(3-氟苯基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(3-氟苯

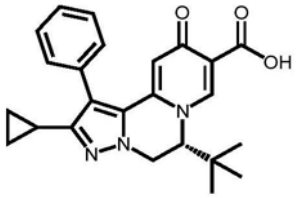
基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(13mg)。ESI MS m/z＝422.1[M+H]$^+$。

[0980] 实施例148:合成(R)-6-(叔丁基)-2-环丙基-1-(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0981] 

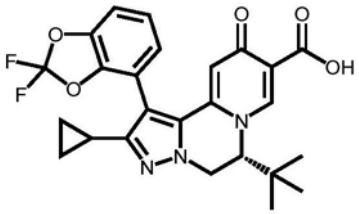
[0982] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(2-氟苯基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(10mg)。ESI MS m/z＝422.1[M+H]$^+$。

[0983] 实施例149:合成(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0984] 

[0985] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用苯基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(9mg)。ESI MS m/z＝404.1[M+H]$^+$。

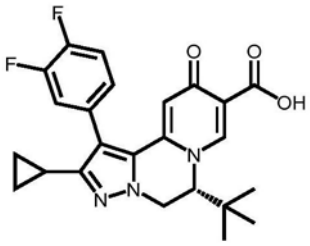
[0986] 实施例150:合成(R)-6-(叔丁基)-2-环丙基-1-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0987] 

[0988] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)硼酸代替噻吩-3-

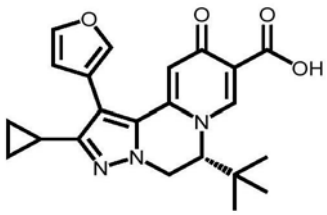
基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(2,2-二氟苯并[d][1,3]二氧杂环戊烯-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(14mg)。ESI MS m/z＝484.1[M+H]$^+$。

[0989] 实施例151:合成(R)-6-(叔丁基)-2-环丙基-1-(3,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0990] 

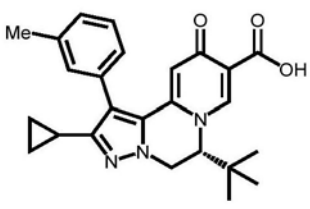
[0991] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(3,4-二氟苯基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(3,4-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z＝440.1[M+H]$^+$。

[0992] 实施例152:合成(R)-6-(叔丁基)-2-环丙基-1-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0993] 

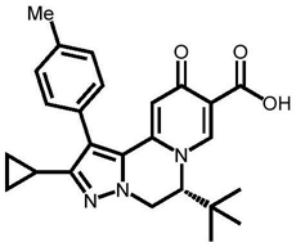
[0994] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用呋喃-3-基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(12mg)。ESI MS m/z＝394.1[M+H]$^+$。

[0995] 实施例153:合成(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(间甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0996] 

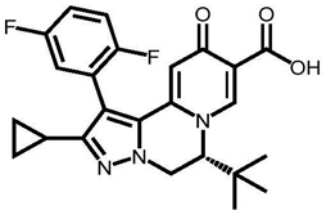
[0997] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用间甲苯基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(间甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝418.1[M+H]$^+$。

[0998] 实施例154:合成(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(对甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[0999] 

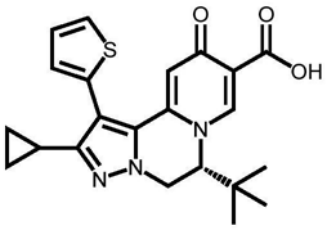
[1000] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用对甲苯基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(对甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(7mg)。ESI MS m/z＝418.1[M+H]$^+$。

[1001] 实施例155:合成(R)-6-(叔丁基)-2-环丙基-1-(2,5-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1002] 

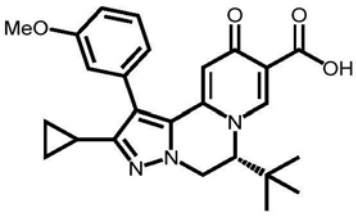
[1003] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(2,5-二氟苯基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(2,5-二氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝440.1[M+H]$^+$。

[1004] 实施例156:合成(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(噻吩-2-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1005] 

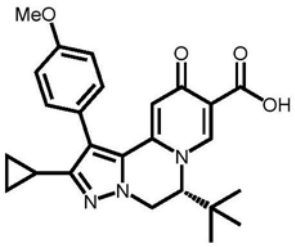
[1006] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用噻吩-2-基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(噻吩-2-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(6mg)。ESI MS m/z＝410.1[M+H]$^+$。

[1007] 实施例157:合成(R)-6-(叔丁基)-2-环丙基-1-(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1008] 

[1009] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用3-甲氧基苯基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(3-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(7mg)。ESI MS m/z＝434.1[M+H]$^+$。

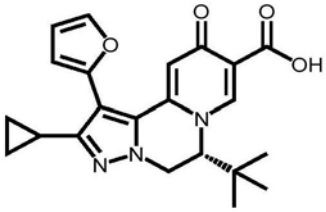
[1010] 实施例158:合成(R)-6-(叔丁基)-2-环丙基-1-(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1011] 

[1012] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(4-甲氧基苯基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(4-甲氧基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸

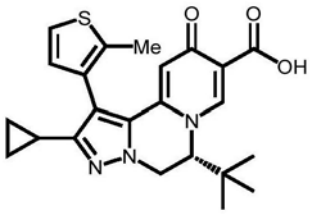
(4mg)。ESI MS m/z＝434.1[M+H]$^+$。

[1013] 实施例159:合成(R)-6-(叔丁基)-2-环丙基-1-(呋喃-2-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1014] 

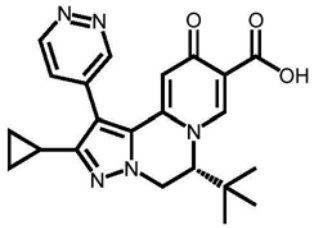
[1015] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用呋喃-2-基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(呋喃-2-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(15mg)。ESI MS m/z＝394.1[M+H]$^+$。

[1016] 实施例160:合成(R)-6-(叔丁基)-2-环丙基-1-(2-甲基噻吩-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1017] 

[1018] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(2-甲基噻吩-3-基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(2-甲基噻吩-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝424.1[M+H]$^+$。

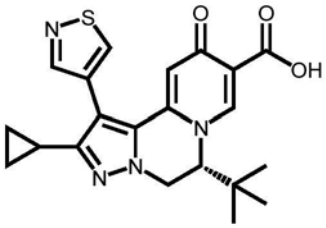
[1019] 实施例161:合成(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(哒嗪-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1020] 

[1021] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用哒嗪-4-基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-

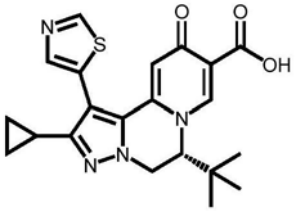
(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(哒嗪-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z=406.1[M+H]$^+$。

[1022] 实施例162:合成(R)-6-(叔丁基)-2-环丙基-1-(异噻唑-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1023] 

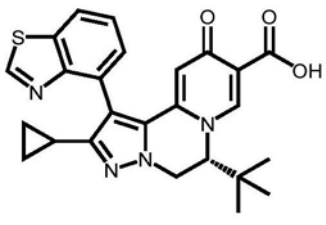
[1024] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用异噻唑-4-基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(异噻唑-4-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(8mg)。ESI MS m/z=411.1[M+H]$^+$。

[1025] 实施例163:合成(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(噻唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1026] 

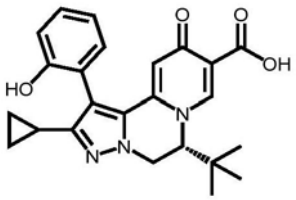
[1027] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用噻唑-5-基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-10-氧亚基-1-(噻唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z=411.1[M+H]$^+$。

[1028] 实施例164:合成(R)-1-(苯并[d]噻唑-4-基)-6-(叔丁基)-2-环丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1029] 

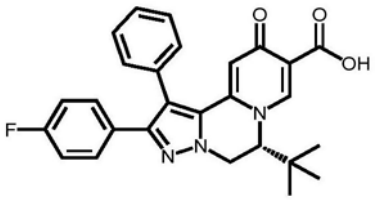
[1030] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用苯并[d]噻唑-4-基硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-1-(苯并[d]噻唑-4-基)-6-(叔丁基)-2-环丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z=461.1[M+H]$^+$。

[1031] 实施例165:合成(R)-6-(叔丁基)-2-环丙基-1-(2-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1032] 

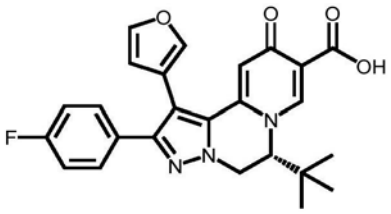
[1033] 用于合成标题分子的程序与用于合成(R)-2-环丙基-6-异丙基-10-氧亚基-1-(噻吩-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例128)的程序相同,除了在步骤7中使用(2-羟基苯基)硼酸代替噻吩-3-基硼酸,以及在步骤1中使用(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替(R)-4-异丙基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(2-羟基苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(6mg)。ESI MS m/z=420.1[M+H]$^+$。

[1034] 实施例166:合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1035] 

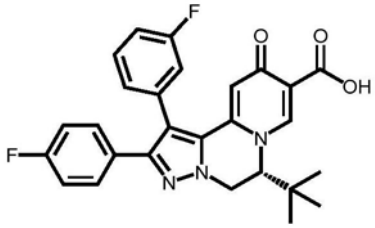
[1036] 步骤1:将苯基硼酸(16mg)、(R)-6-(叔丁基)-1-氯-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例87,27mg)、碳酸铯(61mg)以及Pd-tBuXPhos G3(7mg)在DMF(5mL)中的溶液在100℃下在搅拌下在密封小瓶中加热18h。在冷却至室温之后,将混合物过滤并通过RPHPLC纯化以得到(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(10mg)。ESI MS m/z=458.1[M+H]$^+$。

[1037] 实施例167:合成(R)-6-(叔丁基)-2-(4-氟苯基)-1-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1038] 

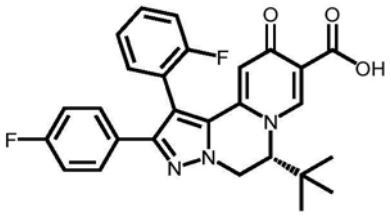
[1039] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例166)的程序相同,除了使用呋喃-3-基硼酸代替苯基硼酸之外,以得到(R)-6-(叔丁基)-2-(4-氟苯基)-1-(呋喃-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝448.1[M+H]$^+$。

[1040] 实施例168:合成(R)-6-(叔丁基)-1-(3-氟苯基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1041] 

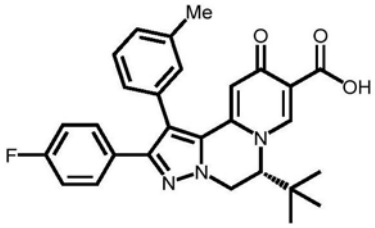
[1042] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例166)的程序相同,除了使用(3-氟苯基)硼酸代替苯基硼酸之外,以得到(R)-6-(叔丁基)-1-(3-氟苯基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(8mg)。ESI MS m/z＝476.1[M+H]$^+$。

[1043] 实施例169:合成(R)-6-(叔丁基)-1-(2-氟苯基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1044] 

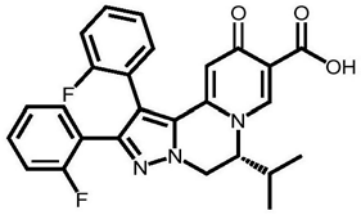
[1045] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例166)的程序相同,除了使用(2-氟苯基)硼酸代替苯基硼酸之外,以得到(R)-6-(叔丁基)-1-(2-氟苯基)-2-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(9mg)。ESI MS m/z＝476.1[M+H]$^+$。

[1046] 实施例170:合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-(间甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1047] 

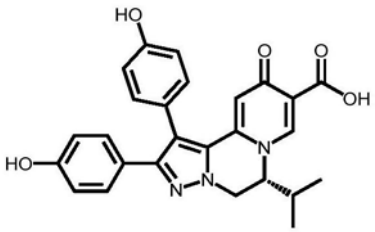
[1048] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例166)的程序相同,除了使用间甲苯基硼酸代替苯基硼酸之外,以得到(R)-6-(叔丁基)-2-(4-氟苯基)-10-氧亚基-1-(间甲苯基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝472.1[M+H]$^+$。

[1049] 实施例171:合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1050] 

[1051] 步骤1:在小瓶中装入(R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(实施例128,步骤5,50.00mg,0.121mmol,1.00当量)、DMF(1.00mL)、2-氟苯基硼酸(84.35mg,0.603mmol,5.00当量)、H_2O(0.25mL)、Cs_2CO_3(112.96mg,0.347mmol,3.00当量)以及XPhos Pd G3(19.56mg,0.023mmol,0.20当量)。将所得混合物在氮气气氛下在120℃下搅拌过夜。将混合物用H_2O稀释,用EtOAc萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,将滤液在减压下浓缩。将粗产物通过RPHPLC纯化以得到(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(10.4mg,18.69%),为浅黄色固体。ESI MS m/z＝462.1[M+H]$^+$。

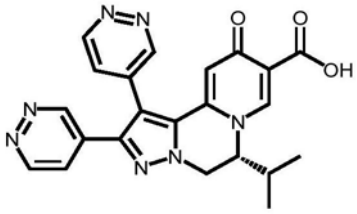
[1052] 实施例172:合成(R)-1,2-双(4-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1053] 

[1054] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用(4-羟基苯基)硼酸代替2-氟苯基硼酸之外,以得到(R)-1,2-双(4-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z＝458.1[M+H]$^+$。

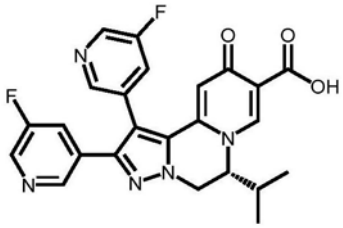
[1055] 实施例173:合成(R)-6-异丙基-10-氧亚基-1,2-二(哒嗪-4-基)-5,6-二氢-10H-

吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1056] 

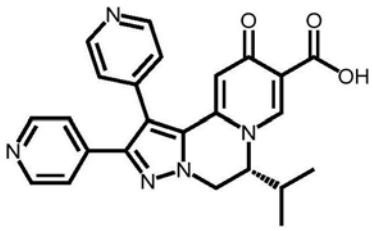
[1057] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用哒嗪-4-基硼酸代替2-氟苯基硼酸之外,以得到(R)-6-异丙基-10-氧亚基-1,2-二(哒嗪-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝430.1[M+H]$^+$。

[1058] 实施例174:合成(R)-1,2-双(5-氟吡啶-3-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1059] 

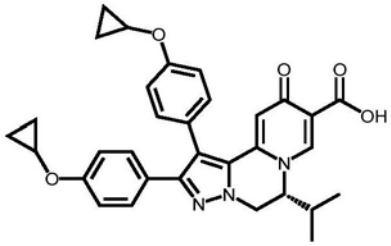
[1060] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用(5-氟吡啶-3-基)硼酸代替2-氟苯基硼酸之外,以得到(R)-1,2-双(5-氟吡啶-3-基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(1mg)。ESI MS m/z＝464.1[M+H]$^+$。

[1061] 实施例175:合成(R)-6-异丙基-10-氧亚基-1,2-二(吡啶-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1062] 

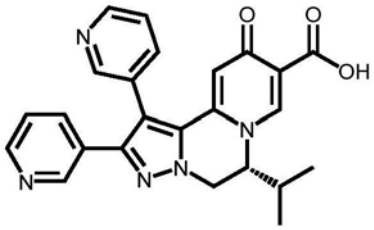
[1063] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用吡啶-4-基硼酸代替2-氟苯基硼酸之外,以得到(R)-6-异丙基-10-氧亚基-1,2-二(吡啶-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝428.1[M+H]$^+$。

[1064] 实施例176:合成(R)-1,2-双(4-环丙氧基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1065] 

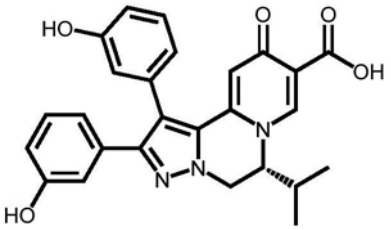
[1066] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用(4-环丙氧基苯基)硼酸代替2-氟苯基硼酸之外,以得到(R)-1,2-双(4-环丙氧基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝538.1[M+H]$^+$。

[1067] 实施例177:合成(R)-6-异丙基-10-氧亚基-1,2-二(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1068] 

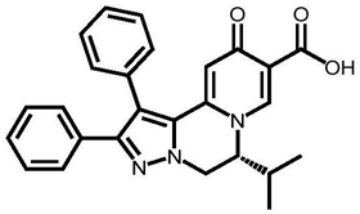
[1069] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用吡啶-3-基硼酸代替2-氟苯基硼酸之外,以得到(R)-6-异丙基-10-氧亚基-1,2-二(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z＝428.1[M+H]$^+$。

[1070] 实施例178:合成(R)-1,2-双(3-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1071] 

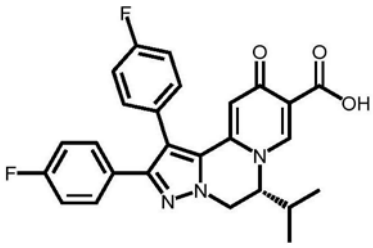
[1072] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用(3-羟基苯基)硼酸代替2-氟苯基硼酸之外,以得到(R)-1,2-双(3-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝458.1[M+H]$^+$。

[1073] 实施例179:合成(R)-6-异丙基-10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1074] 

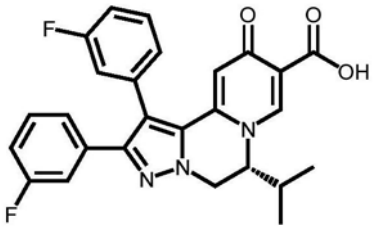
[1075] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用苯基硼酸代替2-氟苯基硼酸之外,以得到(R)-6-异丙基-10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(8mg)。ESI MS m/z＝426.1[M+H]$^+$。

[1076] 实施例180:合成(R)-1,2-双(4-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1077] 

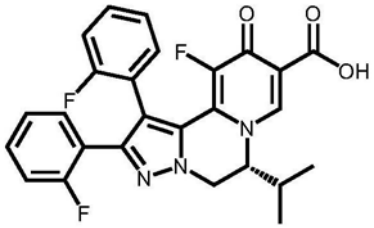
[1078] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用(4-氟苯基)硼酸代替2-氟苯基硼酸之外,以得到(R)-1,2-双(4-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(12mg)。ESI MS m/z＝462.1[M+H]$^+$。

[1079] 实施例181:合成(R)-1,2-双(3-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1080] 

[1081] 用于合成标题分子的程序与用于合成(R)-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例171)的程序相同,除了使用(3-氟苯基)硼酸代替2-氟苯基硼酸之外,以得到(R)-1,2-双(3-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝462.1[M+H]$^+$。

[1082] 实施例182:合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

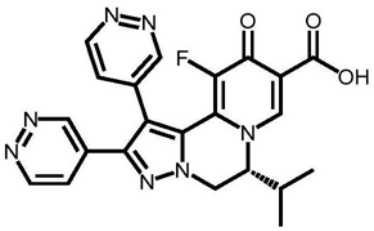
[1083] 

[1084] 步骤1:在氩气气氛下,将Mg(7.83g,322.094mmol,8.00当量)和TMSCl(34.99g,322.094mmol,8.00当量)的混合物用超声波照射处理20min。在氩气气氛下在15℃下,逐滴添加DMF(64.00mL)和(Z)-2-(乙氧基亚甲基)-4,4,4-三氟-3-氧亚基丁酸乙酯(9.67g,40.262mmol,1.00当量)。将所得混合物在氮气气氛下在50℃下搅拌5h。在真空中去除过量的TMSCl之后,将粗混合物过滤,并且滤液(DMF和(Z)-2-(乙氧基亚甲基)-4,4-二氟-3-((三甲基硅烷基)氧基)丁-3-烯酸乙酯)无需进一步纯化即用于下一步骤。

[1085] 步骤2:在20℃下向ZnI_2(4.25g,13.314mmol,1.00当量)和(R)-2-溴-3-氯-6-异丙基-6,7-二氢吡唑并[1,5-a]吡嗪(实施例128,步骤3,3.68g,13.306mmol,1.00当量)在干MeCN(34.00mL)中的悬浮液中逐滴添加粗(Z)-2-(乙氧基亚甲基)-4,4-二氟-3-((三甲基硅烷基)氧基)丁-3-烯酸乙酯(11.75g,39.919mmol,3.00当量)在干DMF(64.00mL)中的溶液。将所得混合物在50℃下搅拌过夜。将混合物用H_2O(100ml)稀释,用EtOAc(3x100ml)萃取。将有机层通过盐水洗涤,用Na_2SO_4干燥并在减压下浓缩。将残余物通过RPHPLC纯化以得到(R)-2-溴-1-氯-11-氟-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(3.4g,59.06%),为深棕色固体。

[1086] 步骤3:向小瓶中添加(R)-2-溴-1-氯-11-氟-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(50.00mg,0.116mmol,1.00当量)、DMF(1.00mL)、(2-氟苯基)硼酸(80.85mg,0.578mmol,5.00当量)、H_2O(0.25mL)、Cs_2CO_3(112.96mg,0.347mmol,3.00当量)以及XPhos Pd G_3(19.56mg,0.023mmol,0.20当量)。将所得混合物在氮气气氛下在120℃下搅拌过夜。将残余物通过RPHPLC纯化以得到(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(9.6mg,17.33%),为黄色固体。ESI MS m/z=480.1$[M+H]^+$。

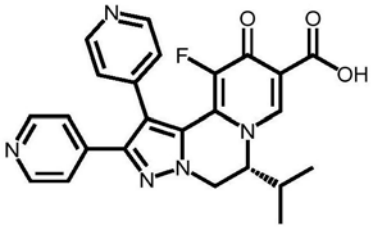
[1087] 实施例183:合成(R)-11-氟-6-异丙基-10-氧亚基-1,2-二(哒嗪-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1088] 

[1089] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用哒嗪-4-基硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-6-异丙基-10-氧亚基-1,2-二(哒嗪-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z=448.1$[M+H]^+$。

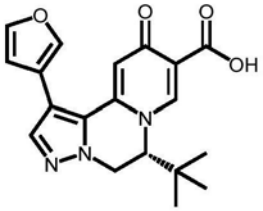
[1090] 实施例184:合成(R)-11-氟-6-异丙基-10-氧亚基-1,2-二(吡啶-4-基)-5,6-二

氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1091] 

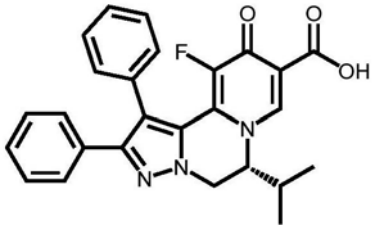
[1092] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用吡啶-4-基硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-6-异丙基-10-氧亚基-1,2-二(吡啶-4-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝446.1[M+H]$^+$。

[1093] 实施例185:合成(R)-1,2-双(3-氯苯基)-11-氟-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1094] 

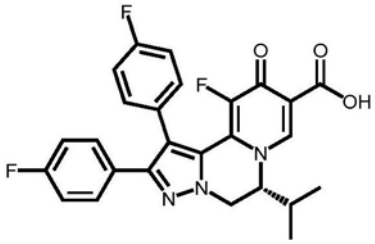
[1095] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用(3-氯苯基)硼酸代替(2-氟苯基)硼酸之外,以得到(R)-1,2-双(3-氯苯基)-11-氟-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z＝512.1[M+H]$^+$。

[1096] 实施例186:合成(R)-11-氟-6-异丙基-10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1097] 

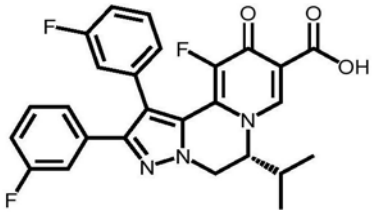
[1098] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用苯基硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-6-异丙基-10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z＝444.1[M+H]$^+$。

[1099] 实施例187:合成(R)-11-氟-1,2-双(4-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1100] 

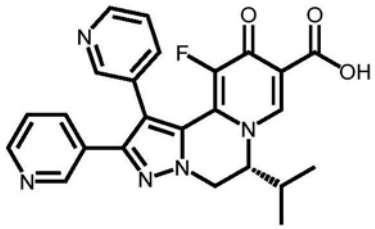
[1101] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用(4-氟苯基)硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-1,2-双(4-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(9mg)。ESI MS m/z＝480.1[M+H]$^+$。

[1102] 实施例188:合成(R)-11-氟-1,2-双(3-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1103] 

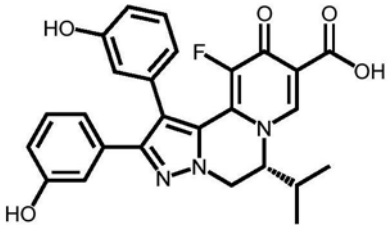
[1104] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用(3-氟苯基)硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-1,2-双(3-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(7mg)。ESI MS m/z＝480.1[M+H]$^+$。

[1105] 实施例189:合成(R)-11-氟-6-异丙基-10-氧亚基-1,2-二(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1106] 

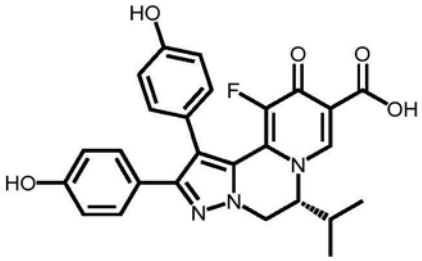
[1107] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用吡啶-3-基硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-6-异丙基-10-氧亚基-1,2-二(吡啶-3-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z＝446.1[M+H]$^+$。

[1108] 实施例190:合成(R)-11-氟-1,2-双(3-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1109] 

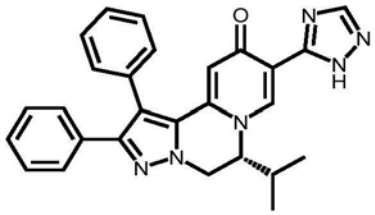
[1110] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用(3-羟基苯基)硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-1,2-双(3-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝476.1[M+H]$^+$。

[1111] 实施例191:合成(R)-11-氟-1,2-双(4-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1112] 

[1113] 用于合成标题分子的程序与用于合成(R)-11-氟-1,2-双(2-氟苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例182)的程序相同,除了使用(4-羟基苯基)硼酸代替(2-氟苯基)硼酸之外,以得到(R)-11-氟-1,2-双(4-羟基苯基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(6mg)。ESI MS m/z＝476.1[M+H]$^+$。

[1114] 实施例192:合成(R)-6-异丙基-1,2-二苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮。

[1115] 

[1116] 步骤1:将(R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(实施例128,步骤5,1.10g,2.653mmol,1.00当量)在NH_3/MeOH(20mL,7M)中的溶液在60℃下搅拌过夜。将溶剂在真空下浓缩以得到(R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(1.02g,99.7%),为棕黄色固体。

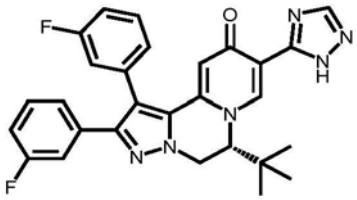
[1117] 步骤2:将(R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(927.50mg,2.4mmol,1.00当量)在DMF-DMA(14.31g,120mmol,50.00当量)在MeCN(10.00mL)中的溶液在60℃下搅拌2h。反应完成之后,将溶剂去除以得到(R,E)-2-溴-1-氯-N-((二甲基氨基)亚甲基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并

[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺和(R)-2-溴-1-氯-N-甲酰基-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(1:3比率,1.48g),为棕色半固体。

[1118] 步骤3:将(R,E)-2-溴-1-氯-N-((二甲基氨基)亚甲基)-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺和(R)-2-溴-1-氯-N-甲酰基-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(1:3比率,1.48g,3.578mmol,1.00当量)和水合肼(895.55mg,17.889mmol,5.00当量)在AcOH中的溶液在95℃下搅拌0.5h。反应完成之后,在减压下去除溶剂。将残余物通过RPHPLC纯化以得到(R)-2-溴-1-氯-6-异丙基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(800mg,54.58%),为棕色固体。

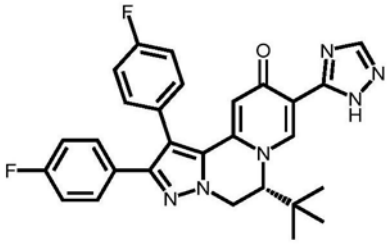
[1119] 步骤4:将(R)-2-溴-1-氯-6-异丙基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(50.00mg,0.122mmol,1.00当量)、苯基硼酸(74.41mg,0.610mmol,5.00当量)、$Pd(PPh_3)_4$(28.21mg,0.024mmol,0.20当量)以及Cs_2CO_3(19.88mg,0.061mmol,5.00当量)在二噁烷(2.00mL)和H_2O(0.40mL)中的溶液在氮气气氛下在120℃下搅拌过夜。将混合物用H_2O(10ml)稀释,用EtOAc(3x20ml)萃取。将有机层通过盐水洗涤,用Na_2SO_4干燥并在减压下浓缩。将残余物通过RPHPLC纯化以得到(R)-6-异丙基-1,2-二苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(23.3mg,40.3%),为白色固体。ESI MS m/z=449.1$[M+H]^+$。

[1120] 实施例193:合成(R)-6-(叔丁基)-1,2-双(3-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮。

[1121] 

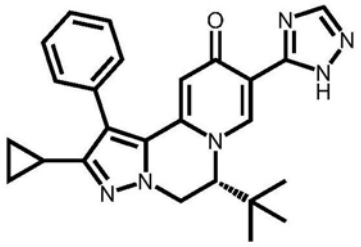
[1122] 用于合成标题分子的程序与用于合成(R)-6-异丙基-1,2-二苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(实施例192)的程序相同,除了在步骤1中使用(R)-2-溴-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(实施例87,步骤3)代替(R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯,以及在步骤4中使用(3-氟苯基)硼酸代替苯基硼酸之外,以得到(R)-6-(叔丁基)-1,2-双(3-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(2mg)。ESI MS m/z=499.1$[M+H]^+$。

[1123] 实施例194:合成(R)-6-(叔丁基)-1,2-双(4-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮。

[1124] 

[1125] 用于合成标题分子的程序与用于合成(R)-6-异丙基-1,2-二苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(实施例192)的程序相同,除了在步骤1中使用(R)-2-溴-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(实施例87,步骤3)代替(R)-2-溴-1-氯-6-异丙基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯,以及在步骤4中使用(4-氟苯基)硼酸代替苯基硼酸之外,以得到(R)-6-(叔丁基)-1,2-双(4-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(9mg)。ESI MS m/z＝499.1[M+H]$^+$。

[1126] 实施例195:合成(R)-6-(叔丁基)-2-环丙基-1-苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮。

[1127] 

[1128] 步骤1:将(R)-2-溴-6-(叔丁基)-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(实施例87,步骤3,500mg)在NH_3/MeOH(10mL,7M)中的溶液在60℃下搅拌过夜。将溶剂在真空下浓缩以得到(R)-2-溴-1-氯-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(490mg),为棕黄色固体。

[1129] 步骤2:将(R)-2-溴-1-氯-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(450mg)在DMF-DMA(7g)和MeCN(5mL)中的溶液在60℃下搅拌2h。反应完成之后,将溶剂去除以得到(R,E)-2-溴-1-氯-N-((二甲基氨基)亚甲基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺和(R)-2-溴-1-氯-N-甲酰基-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(1:3比率,750mg),为棕色半固体。

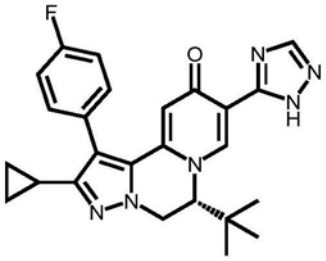
[1130] 步骤3:将(R,E)-2-溴-1-氯-N-((二甲基氨基)亚甲基)-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺和(R)-2-溴-1-氯-N-甲酰基-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酰胺(1:3比率,750mg)和水合肼(400mg)在AcOH中的溶液在95℃下搅拌0.5h。反应完成之后,在减压下去除溶剂。将残余物通过RPHPLC纯化以得到(R)-2-溴-1-氯-6-(叔丁基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(403mg),为棕色固体。

[1131] 步骤4:将(R)-2-溴-1-氯-6-(叔丁基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-

吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(50mg)、环丙基硼酸(25mg)、$Pd(PPh_3)_4$(13mg)以及Cs_2CO_3(78mg)在二噁烷(5ml)和H_2O(1ml)中的混合物在氮气气氛下在100℃下搅拌过夜。将混合物用H_2O(10ml)稀释，用EtOAc(3x20ml)萃取。将有机层通过盐水洗涤，用Na_2SO_4干燥并在减压下浓缩。将残余物通过RPHPLC纯化(H_2O/MeCN，0％至100％，20min)以得到(R)-6-(叔丁基)-1-氯-2-环丙基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(35mg)，为棕色固体。

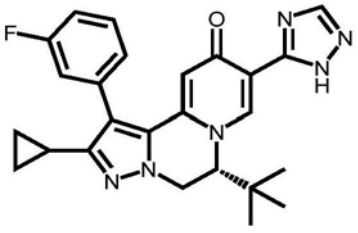
[1132] 步骤5：向(R)-6-(叔丁基)-1-氯-2-环丙基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(50mg)和苯基硼酸(10mg)在DMF(2mL)和H_2O(0.2mL)的溶液中添加Cs_2CO_3(14mg)和Xphos Pd G3(4mg)。在氮气气氛下在120℃下搅拌过夜之后，将混合物用H_2O(10ml)稀释，用EtOAc(3x10ml)萃取。将有机层通过盐水洗涤，用Na_2SO_4干燥并在减压下浓缩。将粗产物通过RPHPLC纯化以得到(R)-6-(叔丁基)-2-环丙基-1-苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(2mg)，为黄色固体。ESI MS m/z＝427.1$[M+H]^+$。

[1133] 实施例196：合成(R)-6-(叔丁基)-2-环丙基-1-(4-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮。

[1134] 

[1135] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-环丙基-1-苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(实施例195)的程序相同，除了使用4-氟苯基硼酸代替苯基硼酸之外，以得到(R)-6-(叔丁基)-2-环丙基-1-(4-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(5mg)。ESI MS m/z＝445.1$[M+H]^+$。

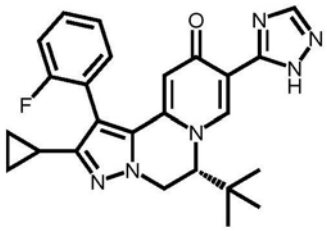
[1136] 实施例197：合成(R)-6-(叔丁基)-2-环丙基-1-(3-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮。

[1137] 

[1138] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-环丙基-1-苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(实施例195)的程序相同，除了使用3-氟苯基硼酸代替苯基硼酸之外，以得到(R)-6-(叔丁基)-2-环丙基-1-(3-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(2mg)。ESI MS m/z＝445.1$[M+H]^+$。

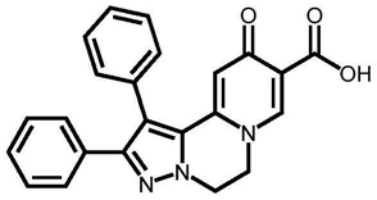
[1139] 实施例198：合成(R)-6-(叔丁基)-2-环丙基-1-(2-氟苯基)-9-(1H-1,2,4-三唑-

5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮。

[1140] 

[1141] 用于合成标题分子的程序与用于合成(R)-6-(叔丁基)-2-环丙基-1-苯基-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(实施例195)的程序相同,除了使用2-氟苯基硼酸代替苯基硼酸之外,以得到(R)-6-(叔丁基)-2-环丙基-1-(2-氟苯基)-9-(1H-1,2,4-三唑-5-基)-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-10-酮(6mg)。ESI MS m/z＝445.1[M+H]$^+$。

[1142] 实施例199:合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1143] 

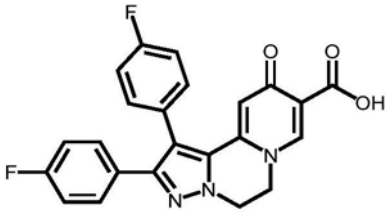
[1144] 步骤1:在氮气下将3,5-二溴-4-氯-1H-吡唑(1g)在THF(10mL)中的溶液冷却至0℃。分批添加60wt%的氢化钠(0.169g)。使混合物在0℃下搅拌直到停止冒泡。在0℃下分批添加1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物(1.3g)。将混合物搅拌5min,然后使其达到室温。将反应混合物搅拌额外的30min,然后向空气开放并用少量的甲醇淬灭。去除挥发物并将残余物溶解在DCM(25mL)中。然后,添加三氟乙酸(10mL)并将所得溶液搅拌15min。去除挥发物并将残余物溶解在乙醇(10mL)和乙酸(5mL)中。然后,4-氧亚基-4H-吡喃-3-甲酸乙酯(1g)作为在乙醇(8mL)中的溶液添加。将混合物加热至回流持续5h。去除挥发物,并将产物在硅胶上纯化(MeOH:EtOAc 0-15%)以得到1-(2-(3,5-二溴-4-氯-1H-吡唑-1-基)乙基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(410mg)。

[1145] 步骤2:在氮气下在微波小瓶中装入1-(2-(3,5-二溴-4-氯-1H-吡唑-1-基)乙基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(100mg)、新戊酸铯(120mg)、溴化钯(II)(50mg)以及DMF(10mL)。使氮气通过所得溶液鼓泡10min。将所得溶液在微波中在120℃下加热60min。将所得溶液过滤、浓缩并在硅胶上纯化(MeOH:EtOAc 0-15%)以得到2-溴-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(55mg)。

[1146] 步骤3:将2-溴-1-氯-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(25mg)、苯基硼酸(100mg)、碳酸铯(60mg)以及Pd-tBuXPhos G3(5mg)在1,4-二噁烷(5mL)和水(1mL)中的溶液在100℃下在搅拌下在密封小瓶中加热18h。冷却至室温之后,添加二氯甲烷和1N HCl。将反应混合物用二氯甲烷萃取并将有机层浓缩。将残余物通过RPHPLC纯化以得到10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z＝384.1[M+H]$^+$。

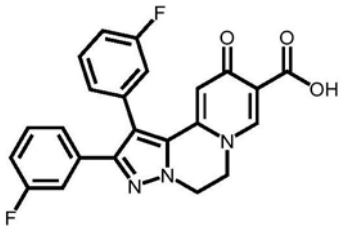
[1147] 实施例200:合成1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡

啶并[2,1-c]吡嗪-9-甲酸。

[1148] 

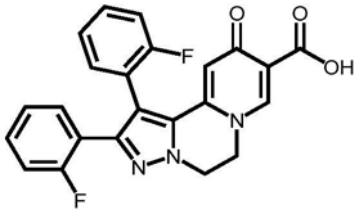
[1149] 用于合成标题分子的程序与用于合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例199)的程序相同,除了使用(4-氟苯基)硼酸代替苯基硼酸之外,以得到1,2-双(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z＝420.1[M+H]$^+$。

[1150] 实施例201:合成1,2-双(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1151] 

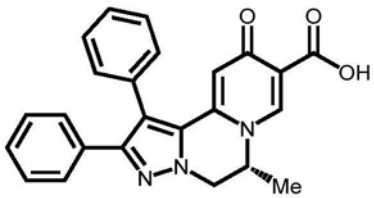
[1152] 用于合成标题分子的程序与用于合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例199)的程序相同,除了使用(4-氟苯基)硼酸代替苯基硼酸之外,以得到1,2-双(3-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z＝420.1[M+H]$^+$。

[1153] 实施例202:合成1,2-双(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1154] 

[1155] 用于合成标题分子的程序与用于合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例199)的程序相同,除了使用(2-氟苯基)硼酸代替苯基硼酸之外,以得到1,2-双(2-氟苯基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(3mg)。ESI MS m/z＝420.1[M+H]$^+$。

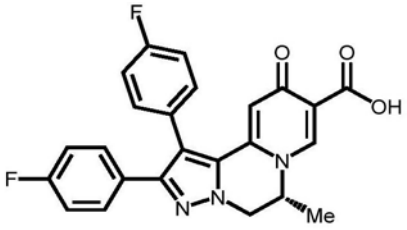
[1156] 实施例203:合成(R)-6-甲基-10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1157] 

[1158] 用于合成标题分子的程序与用于合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡

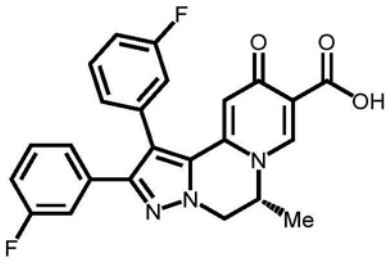
唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例199)的程序相同,除了在步骤1中使用(R)-4-甲基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-6-甲基-10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(5mg)。ESI MS m/z=398.1[M+H]$^+$。

[1159] 实施例204:合成(R)-1,2-双(4-氟苯基)-6-甲基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1160] 

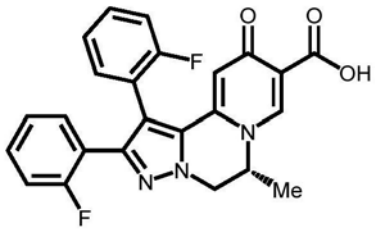
[1161] 用于合成标题分子的程序与用于合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例199)的程序相同,除了在步骤3中使用(4-氟苯基)硼酸代替苯基硼酸,以及在步骤1中使用(R)-4-甲基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-1,2-双(4-氟苯基)-6-甲基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z=434.1[M+H]$^+$。

[1162] 实施例205:合成(R)-1,2-双(3-氟苯基)-6-甲基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1163] 

[1164] 用于合成标题分子的程序与用于合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例199)的程序相同,除了在步骤3中使用(3-氟苯基)硼酸代替苯基硼酸,以及在步骤1中使用(R)-4-甲基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-1,2-双(3-氟苯基)-6-甲基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(2mg)。ESI MS m/z=434.1[M+H]$^+$。

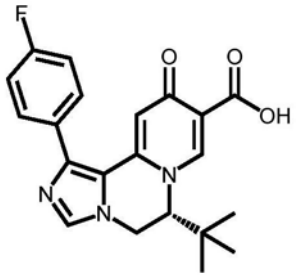
[1165] 实施例206:合成(R)-1,2-双(2-氟苯基)-6-甲基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1166] 

[1167] 用于合成标题分子的程序与用于合成10-氧亚基-1,2-二苯基-5,6-二氢-10H-吡

唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(实施例199)的程序相同,除了在步骤3中使用(2-氟苯基)硼酸代替苯基硼酸,以及在步骤1中使用(R)-4-甲基-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物代替1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物之外,以得到(R)-1,2-双(2-氟苯基)-6-甲基-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(4mg)。ESI MS m/z＝434.1[M+H]$^+$。

[1168] 实施例207:合成(R)-6-(叔丁基)-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1169] 

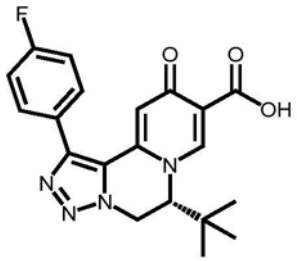
[1170] 步骤1:在烧瓶中装入碳酸铯(670mg)、4-溴-1H-咪唑-5-甲醛(300mg)和DMA(10mL)。然后,添加(R)-4-(叔丁基)-1,2,3-氧杂噻唑烷-3-甲酸叔丁酯2,2-二氧化物(480mg)并将反应混合物在室温下搅拌16h。然后,添加6M的HCl水溶液(20mL)并将混合物搅拌2h,然后过滤。将滤液浓缩并通过RPHPLC纯化以得到(R)-1-溴-6-(叔丁基)-5,6-二氢咪唑并[1,5-a]吡嗪(190mg)。

[1171] 步骤2:在小瓶中装入(R)-1-溴-6-(叔丁基)-5,6-二氢咪唑并[1,5-a]吡嗪(188mg)、(E)-2-(乙氧基亚甲基)-3-氧亚基丁酸乙酯(410mg)以及EtOH(5mL)。将反应混合物加热至95℃持续18h。在冷却至室温之后,将混合物浓缩并无需进一步纯化即直接用于下一步骤。

[1172] 步骤3:将(6R)-1-溴-6-(叔丁基)-10-氧亚基-5,6,11,11a-四氢-10H-咪唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(166mg)和对氯醌(180mg)在DME中的溶液在70℃下搅拌3h。将混合物浓缩并通过RPHPLC纯化以得到(R)-1-溴-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(120mg)。

[1173] 步骤4:在小瓶中装入(4-氟苯基)硼酸(64mg)、(R)-1-溴-6-(叔丁基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(120mg)、XPhos-Pd-G3(50mg)以及碳酸铯(300mg)。用氮气吹扫小瓶5min,然后添加1,4-二噁烷(5mL)和水(1mL)。将小瓶加热至90℃持续2h。然后,使反应达到室温。添加MeOH(5mL)和5M的NaOH水溶液(1.5mL)。在1h之后,用1M的HCl水溶液将pH调节至3,并将产物用乙酸乙酯萃取。将合并的有机部分浓缩并将残余物在RPHPLC上纯化以得到(R)-6-(叔丁基)-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-咪唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(60mg)。ESI MS m/z＝382.1[M+H]$^+$。

[1174] 实施例208:合成(R)-6-(叔丁基)-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,3]三唑并[5,1-c]吡嗪-9-甲酸。

[1175] 

[1176] 步骤1:在烧瓶中装入(R)-2-氨基-3,3-二甲基丁-1-醇(3g)、4-氧亚基-4H-吡喃-3-甲酸乙酯(4.5g)、EtOH(25mL)以及AcOH(12.5mL)。将反应混合物加热至75℃持续5h。在冷却至室温之后,将混合物浓缩,并将残余物在硅胶上纯化(0-30%MeOH/EtOAc)以得到(R)-1-(1-羟基-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(3.8g)。

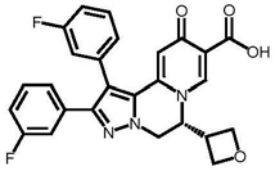
[1177] 步骤2:在烧瓶中装入DIPEA(950mg)、(R)-1-(1-羟基-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(655mg)、DMAP(45mg)以及DCM(15mL)。然后,在0℃下添加甲磺酰氯(340mg)。在30min之后,添加水(10mL)。将有机层用DCM萃取并浓缩。将残余物溶解在DMSO(10mL)中。然后在室温下添加叠氮化钠(480mg)。将混合物温热至80℃持续72h。在冷却至室温之后,将反应混合物用水(10mL)和饱和$NaHCO_3$(10mL)稀释。将产物用DCM萃取,用盐水洗涤,浓缩,并且无需进一步纯化即直接用于下一步骤。

[1178] 步骤3:在烧瓶中装入(R)-1-(1-叠氮基-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(150mg)和THF(5mL)。然后,添加三[(1-苄基-1H-1,2,3-三唑-4-基)甲基]胺(25mg)、碘化钾(340mg)以及高氯酸铜(II)六水合物(380mg)。然后,添加三乙胺(58mg)和1-乙炔基-4-氟苯(125mg)。将反应混合物在室温下向空气开放搅拌16h。将反应用EtOAc(2mL)、水(2mL)和饱和氯化铵水溶液(2mL)稀释。将反应混合物通过硅藻土过滤,然后将有机层分离并浓缩。将残余物在硅胶上纯化(50%EtOAc/己烷)以得到(R)-1-(1-(4-(4-氟苯基)-5-碘-1H-1,2,3-三唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(65mg)。

[1179] 步骤4:在小瓶中装入新戊酸铯(75mg)、溴化钯(II)(30mg)、(R)-1-(1-(4-(4-氟苯基)-5-碘-1H-1,2,3-三唑-1-基)-3,3-二甲基丁-2-基)-4-氧亚基-1,4-二氢吡啶-3-甲酸乙酯(60mg)以及DMF(1.5mL)。将混合物在微波中在120℃下加热1h。将混合物过滤并浓缩,然后通过RPHPLC纯化以得到(R)-6-(叔丁基)-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,3]三唑并[5,1-c]吡嗪-9-甲酸乙酯(20mg)。

[1180] 步骤5:在小瓶中装入(R)-6-(叔丁基)-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,3]三唑并[5,1-c]吡嗪-9-甲酸乙酯(20mg)、THF(2mL)、MeOH(2mL)和3M的NaOH水溶液(1mL)。将反应混合物搅拌1h,然后用3M的HCl水溶液将pH调节至3。将产物用EtOAc萃取并浓缩。将残余物通过RPHPLC纯化以得到(R)-6-(叔丁基)-1-(4-氟苯基)-10-氧亚基-5,6-二氢-10H-吡啶并[1,2-a][1,2,3]三唑并[5,1-c]吡嗪-9-甲酸(9mg)。ESI MS m/z=383.1$[M+H]^+$。

[1181] 实施例209:合成(R)-1,2-双(3-氟苯基)-6-(氧杂环丁-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸。

[1182] 

[1183] 步骤1:在0℃下向3,5-二溴-4-氯-1H-吡唑(2.49g,9.57mmol,1.10当量)在THF中的搅拌溶液中分批添加NaH(0.70g,17.40mmol,2.0当量,60%)。在0℃下向上述混合物中添加4-(氧杂环丁-3-基)-3-三苯甲基-1,2,3-氧杂噻唑烷2,2-二氧化物(3.67g,8.70mmol,1.00当量)。将所得混合物在50℃下搅拌过夜。将反应在室温下用水淬灭。将所得混合物用EtOAc(3x50mL)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,将滤液在减压下浓缩以得到2-(3,5-二溴-4-氯-1H-吡唑-1-基)-1-(氧杂环丁-3-基)-N-三苯甲基乙-1-胺(6.0g,粗品),为黄色固体。粗产物无需进一步纯化即直接用于下一步骤。

[1184] 步骤2:在-40℃下在氮气气氛下,向2-(3,5-二溴-4-氯-1H-吡唑-1-基)-1-(氧杂环丁-3-基)-N-三苯甲基乙-1-胺(6.0g,10.00mmol,1.00当量)在THF中的搅拌溶液中逐滴添加氯(异丙基)镁(30mL,30.00mmol,3.00当量,1M)。在-40℃下向上述混合物中逐滴添加DMF(8.7g,100.00mmol,10.00当量)。将所得混合物在-40℃下搅拌额外的1h。将反应在室温下用饱和NH_4Cl(水溶液)淬灭。将所得混合物用EtOAc(3x50mL)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,将滤液在减压下浓缩以得到3-溴-4-氯-1-(2-(氧杂环丁-3-基)-2-(三苯甲基氨基)乙基)-1H-吡唑-5-甲醛(6.30g,粗品),为黄色油。

[1185] 步骤3:将3-溴-4-氯-1-(2-(氧杂环丁-3-基)-2-(三苯甲基氨基)乙基)-1H-吡唑-5-甲醛(6.30g,11.43mmol,1.00当量)在TFA(5.00mL)和DCM(25.00mL)中的溶液在0℃下搅拌1h。用饱和Na_2CO_3将混合物的pH调至8,用EtOAc(3x50mL)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥。过滤之后,将滤液在减压下浓缩。将残余物通过RPHPLC纯化以得到2-溴-3-氯-6-(氧杂环丁-3-基)-6,7-二氢吡唑并[1,5-a]吡嗪(550mg),为黄色固体。

[1186] 步骤4:将2-溴-3-氯-6-(氧杂环丁-3-基)-6,7-二氢吡唑并[1,5-a]吡嗪(550mg,1.89mmol,1.00当量)和(Z)-2-(乙氧基亚甲基)-3-氧亚基丁酸乙酯(1.05g,5.67mmol,3.00当量)在EtOH中的溶液在回流下搅拌过夜。将混合物浓缩并通过RPHPLC纯化以得到2-溴-1-氯-6-(氧杂环丁-3-基)-10-氧亚基-5,6,11,11a-四氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(370mg,45%),为黄色油。

[1187] 步骤5:将2-溴-1-氯-6-(氧杂环丁-3-基)-10-氧亚基-5,6,11,11a-四氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(370mg,0.86mmol,1.00当量)和对氯醌(432mg,1.72mmol,2.00当量)在DME中的溶液在70℃下搅拌2h。将混合物浓缩并通过RPHPLC纯化以得到2-溴-1-氯-6-(氧杂环丁-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(170mg,46%),为黄色油。

[1188] 步骤6:向小瓶中添加二噁烷(1.50mL)、2-溴-1-氯-6-(氧杂环丁-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸乙酯(75.00mg,0.175mmol,1.00当量)、(3-氟苯基)硼酸(122.40mg、0.875mmol、5.00当量)、Cs_2CO_3(171.02mg,0.525mmol,3当量)、H_2O(0.15mL)和$Pd(PPh_3)_4$(40.44mg,0.035mmol,0.2当量)。将所得混合物在氮气气氛下在120℃下搅拌过夜。将混合物用H_2O(10ml)稀释,用EtOAc(3x20ml)萃取。将有机层通过盐水洗涤,用Na_2SO_4干燥并在减压下浓缩。将残余物通过SFC纯化以得到(R)-

1,2-双(3-氟苯基)-6-(氧杂环丁-3-基)-10-氧亚基-5,6-二氢-10H-吡唑并[1,5-a]吡啶并[2,1-c]吡嗪-9-甲酸(25mg,30.05%),为浅黄色固体。ESI MS m/z＝476.1$[M+H]^+$。

[1189] 生物活性

[1190] 方法:

[1191] 在存在10%FBS、Penn/Strep和250ug/mL G418的DMEM/F12培养基中实现汇合(confluency)后传代2.2.15细胞。将新颖的化合物在DMSO中连续稀释5倍,并以1:200的稀释度添加到包含35,000个细胞/孔的96孔板中,使得DMSO的最终浓度为0.5%。在第5天,收获处理后的细胞裂解物和上清液用于分析。

[1192] 使用Agilent Sidestep裂解缓冲液裂解细胞,以1:100稀释,并通过实时定量PCR定量。在稀释样品以匹配其各自测定的线性范围后,通过遵循制造商推荐的方案,使用可商购的ELISA试剂盒来定量病毒蛋白HBsAg(Alpco)或HBeAg(US Biological)。无论读数如何,报道了相对于无药物对照,将细胞裂解物或上清液中病毒产物积累减少50%的化合物浓度(EC_{50});EC_{50}范围如下:A<0.1μM;B 0.2-1μM;C>1μM。

[1193] 此外,通过将以5,000个细胞/孔接种的HepG2细胞暴露于连续稀释的化合物(最终DMSO浓度为0.5%)三天来估计化合物诱导的细胞毒性。在第3天,根据制造商的说明,用ATPlite 1Step处理接种后的细胞。报道了相对于无药物对照,将孔中的总ATP水平减少50%的化合物浓度(CC_{50});CC_{50}范围如下:A>25μM;B 10-25μM;C<10μM。

[1194] 表2.活性总结

[1195]

实施例编号	2.2.15 细胞 EC_{50} (μM)	HepG2 细胞 CC_{50} (μM)	实施例编号	2.2.15 细胞 EC_{50} (μM)	HepG2 细胞 CC_{50} (μM)
1	A	A	2	A	A
3	A	A	4	B	A
5	A	A	6	A	A
7	B	A	8	A	A
9	A	A	10	A	A
11	A	A	12	A	A
13	A	A	14	B	A
15	A	A	16	A	A
17	A	A	18	A	A
19	A	A	20	A	A
21	A	A	22	A	A
23	B	A	24	A	A
25	B	A	26	A	A
27	A	A	28	A	A
29	A	A	30	A	A
31	A	A	32	A	A
33	A	A	34	A	A
35	B	A	36	A	A
37	A	A	38	A	A
39	A	A	40	A	A
41	A	A	42	A	A
43	A	A	44	A	A
45	A	A	46	A	A
47	A	A	48	A	A
49	B	A	50	B	A
51	B	A	52	B	A
53	B	A	54	A	A
55	A	A	56	A	A
57	A	A	58	A	A
59	A	A	60	A	A
61	A	A	62	B	A

[1196]

63	A	A	64	A	A
65	A	A	66	A	A
67	A	A	68	A	A
69	A	A	70	B	A
71	A	A	72	A	A
73	A	A	74	A	A
75	A	A	76	A	A
77	A	A	78	A	A
79	A	A	80	A	A
81	A	A	82	A	A
83	B	A	84	B	A
85	B	A	86	A	A
87	A		88	A	A
89	A		90	B	
91	A	A	92	A	
93	A	A	94	A	A
95	A	A	96	A	A
97	A	A	98	A	A
99	B		100	A	A
101	A	A	102	A	A
103	A	A	104	A	B
105	B		106	A	
107	A	C	108	A	B
109	A	A	110	A	C
111	A	A	112	A	A
113	A	A	114	A	A
115	A	A	116	A	A
117	C		118	A	
119	A		120	C	
121	C		122	A	A
123	A	A	124	A	
125	A	A	126	A	A
127	A	A	128	A	A
129	A	A	130	A	A
131	A	A	132	A	A
133	A	A	134	A	A
135	A		136	A	A
137	B		138	A	
139	B		140	A	A
141	A		142	A	A
143	A	A	144	A	
145	B		146	A	A
147	A	A	148	A	A
149	A	A	150	A	A
151	A	A	152	A	A
153	A	B	154	A	A
155	A	A	156	A	A
157	A	A	158	A	A

[1197]

159	A	A	160	A	A
161	B		162	A	A
163	A	A	164	A	A
165	A	A	166	A	A
167	A		168	A	B
169	A	B	170	A	B
171	A	A	172	A	A
173	B		174	B	
175	B		176	B	
177	B		178	A	
179	A	A	180	A	B
181	A	B	182	A	A
183	B		184	B	
185	B		186	A	A
187	A	B	188	A	A
189	B		190	B	
191	A	A	192	A	A
193	A	A	194	A	B
195	A	A	196	A	A
197	A	A	198	A	A
199	A	A	200	A	
201	A	A	202	A	
203	A	A	204	A	A
205	A	B	206	A	B
207	A	A	208	A	A
209	A	A			

[1198] 尽管已经参照本发明的优选实施方式特别示出和描述了本发明，但是本领域技术人员将理解，在不脱离所附权利要求所涵盖的本发明范围的情况下，可以在本文中作出形式和细节上的各种改变。