(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 110573499 B
(45)授权公告日 2023.04.21

(21)申请号 201880028013.6
(22)申请日 2018.02.27
(65)同一申请的已公布的文献号
申请公布号 CN 110573499 A
(43)申请公布日 2019.12.13
(30)优先权数据
62/464693 2017.02.28 US
(85)PCT国际申请进入国家阶段日
2019.10.28
(86)PCT国际申请的申请数据
PCT/US2018/019838 2018.02.27
(87)PCT国际申请的公布数据
WO2018/160521 EN 2018.09.07
(73)专利权人 莫菲克医疗股份有限公司
地址 美国马萨诸塞州
(72)发明人 M.布鲁尔 M.G.伯萨维奇
A.L.格拉斯余托 K.N.哈恩
B.A.哈里森 K.D.孔策 林富扬
B.S.利帕 A.A.卢戈夫斯科
B.N.罗杰斯 M.A.斯文森
D.M.特罗亚斯特
(74)专利代理机构 北京品源专利代理有限公司
11332
专利代理师 刘明海 胡彬
(51)Int.Cl.
C07D 401/12(2006.01)
C07D 471/04(2006.01)
(56)对比文件
CN 1209060 A,1999.02.24
CN 1215391 A,1999.04.28
WO 9808840 A1,1998.03.05
CN 106132964 A,2016.11.16
CN 1209063 A,1999.02.24
US 6358970 B1,2002.03.19
US 6232308 B1,2001.05.15
CN 101861319 A,2010.10.13
CN 1073169 A,1993.06.16
CN 104640857 A,2015.05.20
WO 9818460 A1,1998.05.07
Robert S. Meissner等.Nonpeptide αvβ3 Antagonists. Part 2: Constrained Glycyl Amides Derived from the RGD Tripeptide.《Bioorganic & Medicinal Chemistry Letters》.2003,25-29.
STN.RN 2038980-05-9等.《REGISTRY》.2016,1-7.
审查员 张旋

权利要求书67页 说明书178页 附图2页

(54)发明名称

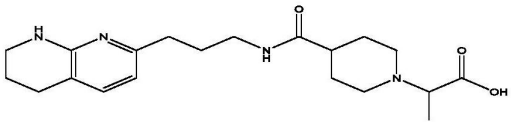
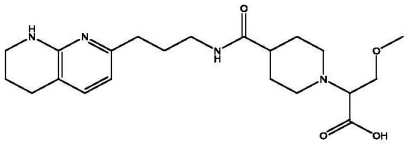
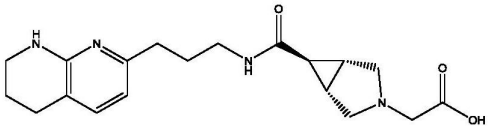
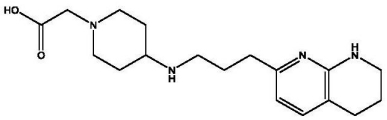
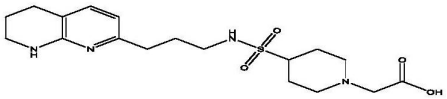
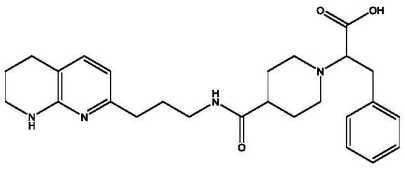
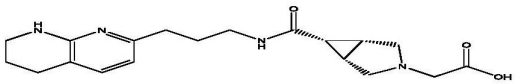
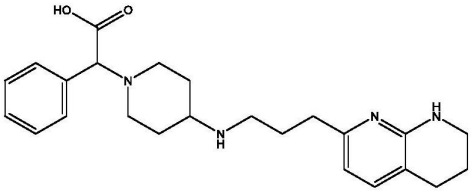
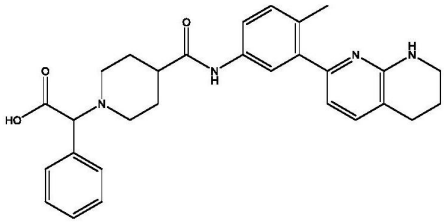
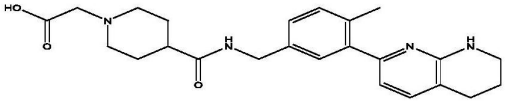
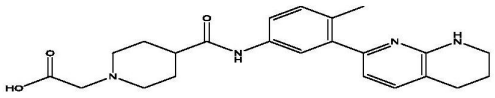
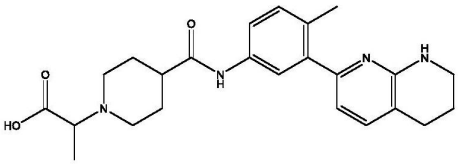
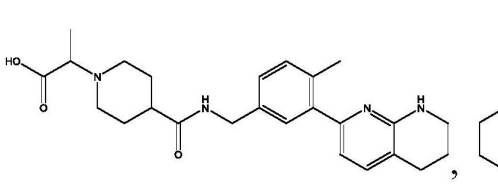
αvβ6整合蛋白的抑制剂

(57)摘要

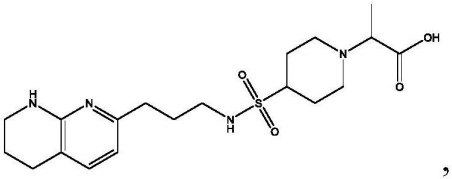
本发明公开αvβ6整合蛋白的小分子抑制剂,和使用其治疗许多疾病和病状的方法。

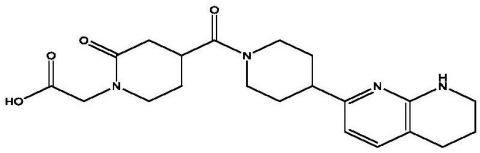
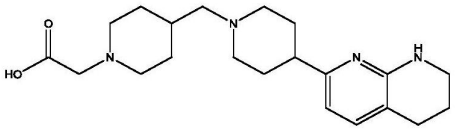
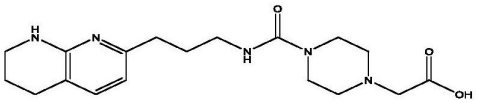
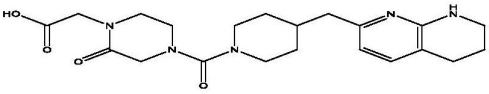
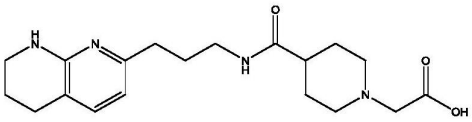
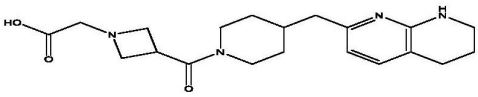
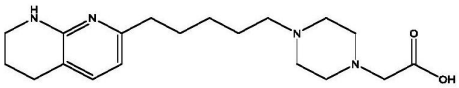
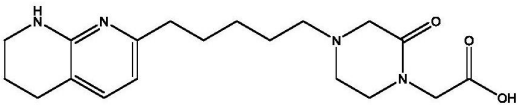
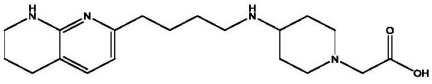
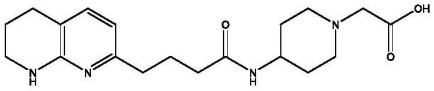
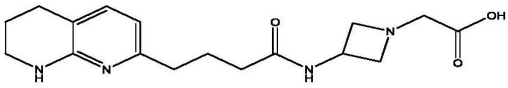
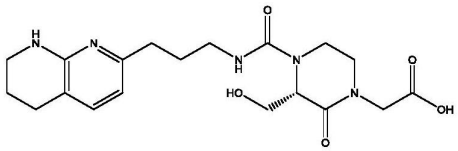
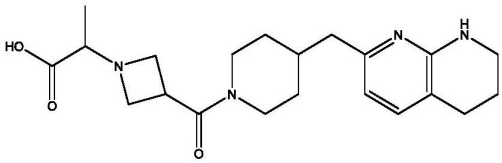
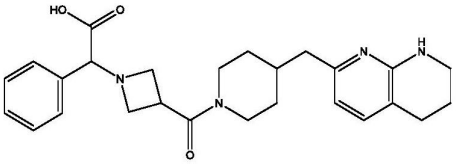
CN 110573499 B

1.一种化合物,其选自由如下组成的组:


,

,

,

,

,

,

,

,

,

,

,

,

,

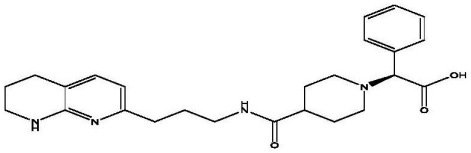
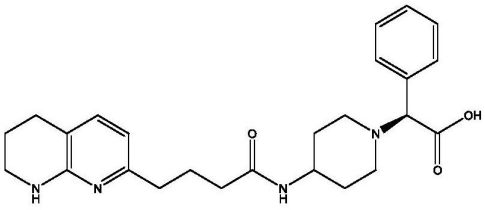
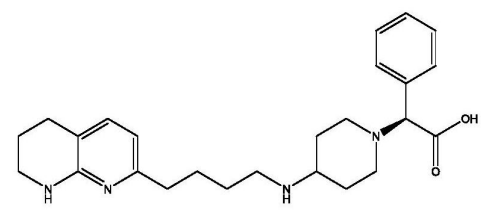
,

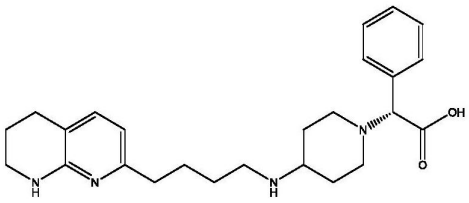
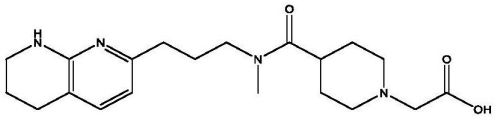
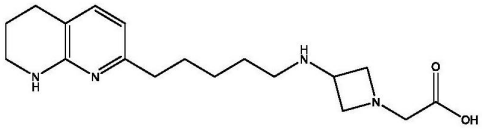
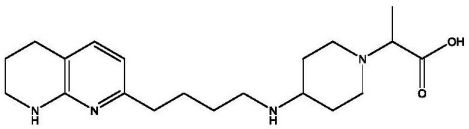
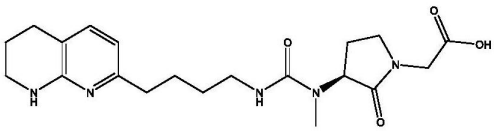
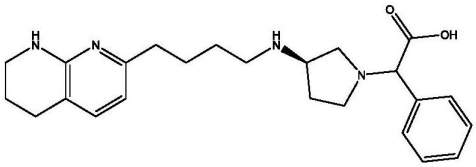
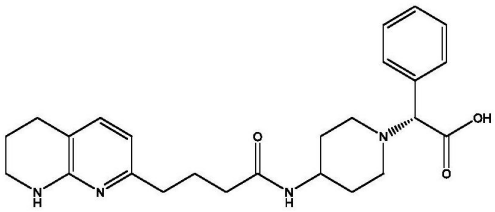
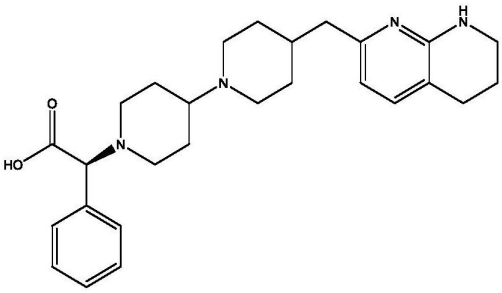
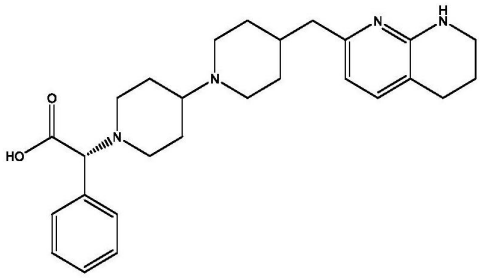
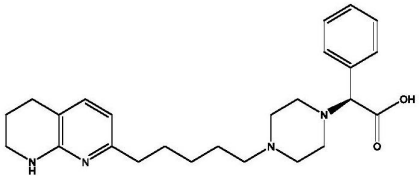
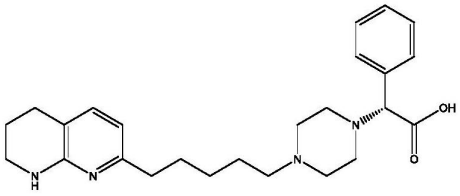
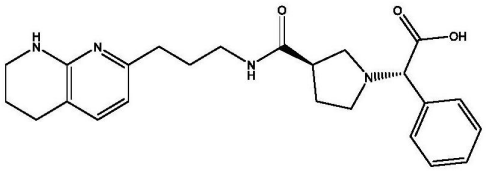
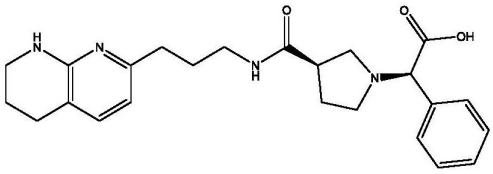
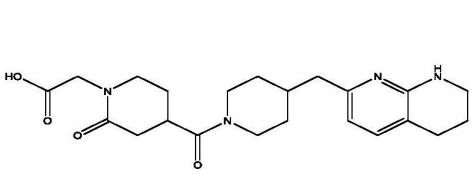
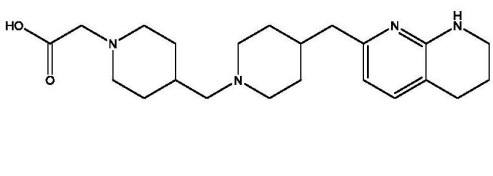
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

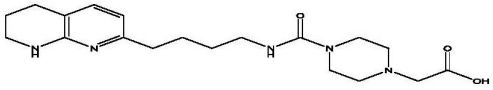
,

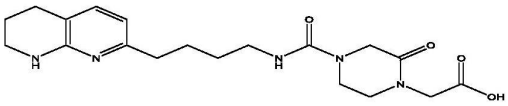
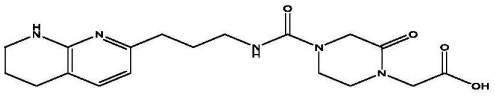
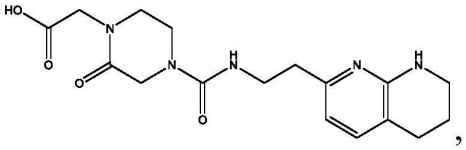
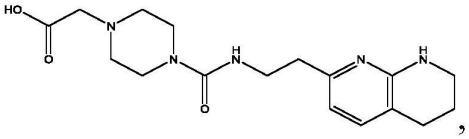
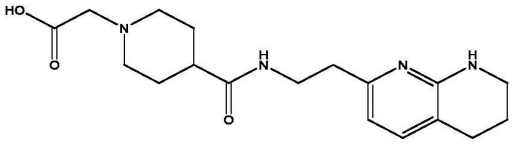
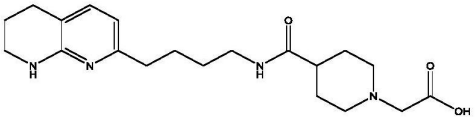
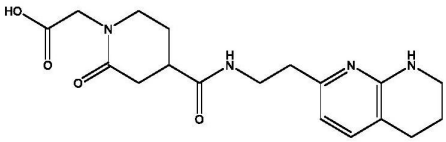
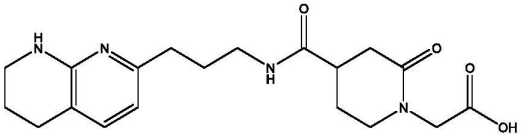
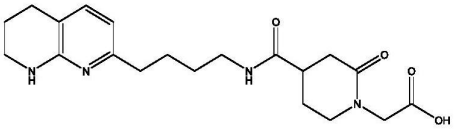
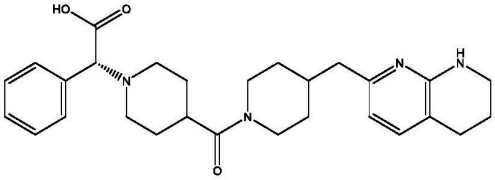
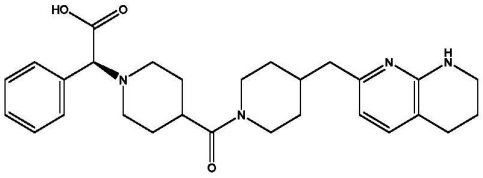
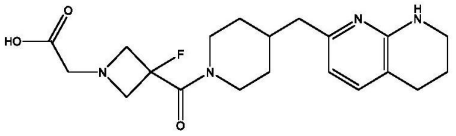
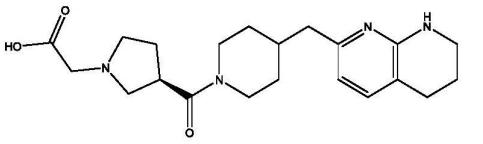
,

,

,

,

,

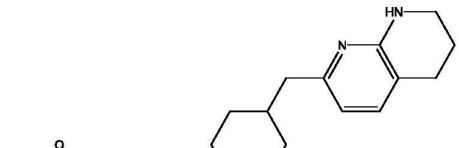
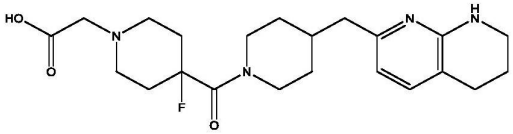

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

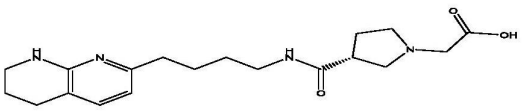
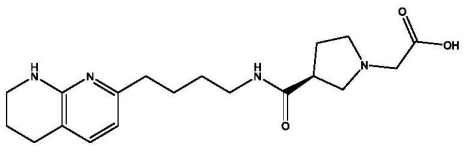
,

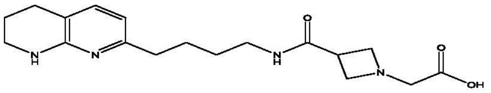
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

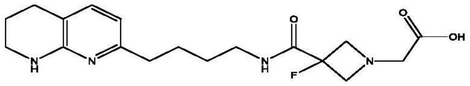
,

,

,

,

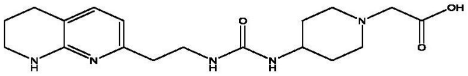
,

,

,


N
H
N
H
N
O
N
O
OH

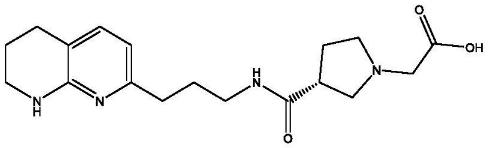
,


N
H
N
H
N
O
F
N
O
OH

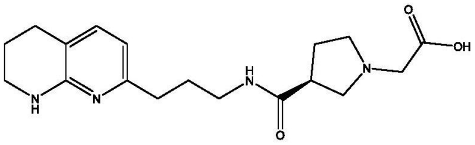
,


N
H
N
H
N
O
H
N
N
OH
O

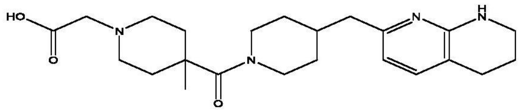
,


N
H
N
H
N
O
N
O
OH

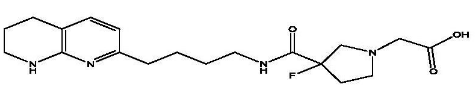
,


N
H
N
H
N
O
N
O
OH

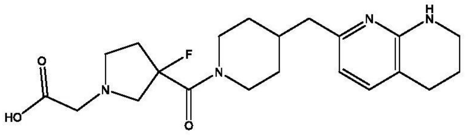
,


HO
O
N
O
N
N
N
H

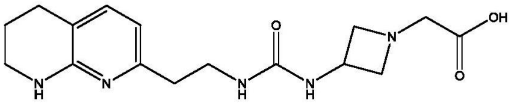
,


N
H
N
H
N
O
F
N
O
OH

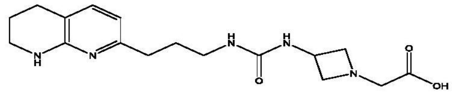
,


O
HO
N
F
O
N
N
N
H

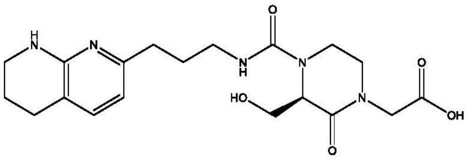
,


N
H
N
H
N
O
H
N
N
OH
O

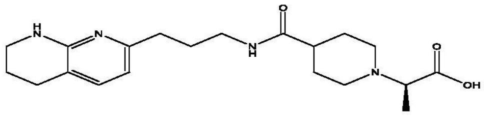
,


N
H
N
H
N
O
H
N
N
O
OH

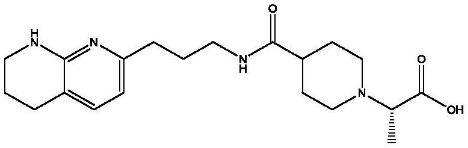
,


H
N
N
H
N
O
N
HO
O
N
O
OH

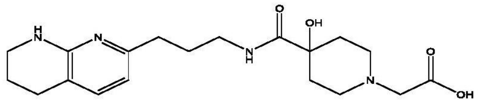
,


H
N
N
H
N
O
N
O
OH

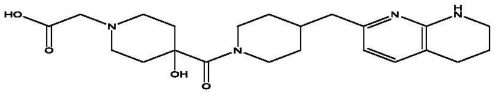
,


H
N
N
H
N
O
N
O
OH

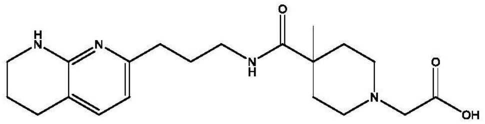
,


H
N
N
H
N
O
OH
N
O
OH

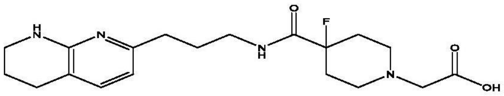
,


HO
O
N
OH
O
N
N
H
N

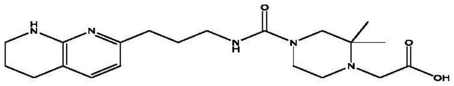
,


H
N
N
H
N
O
N
O
OH

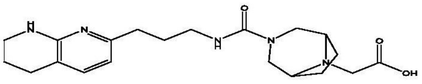
,


H
N
N
H
N
O
F
N
O
OH

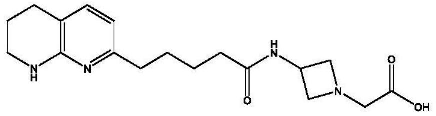
,


H
N
N
H
N
O
N
N
O
OH

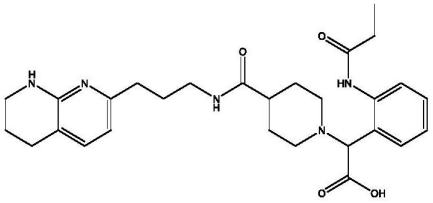
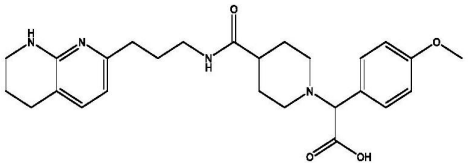
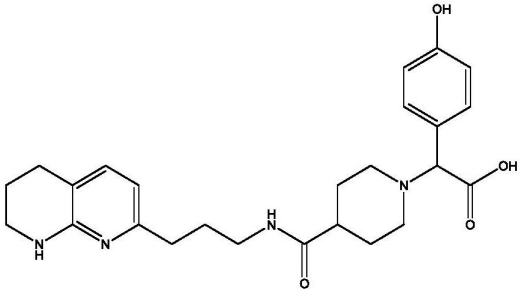
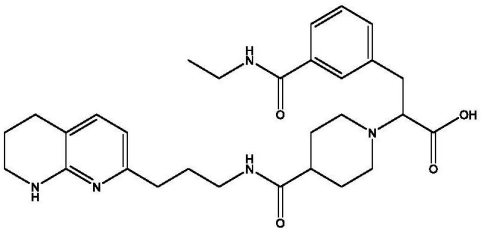
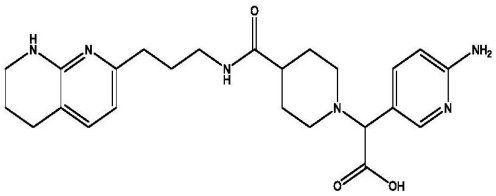
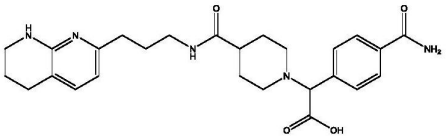
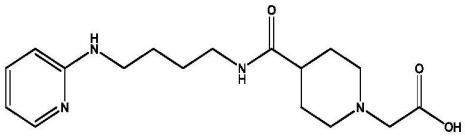
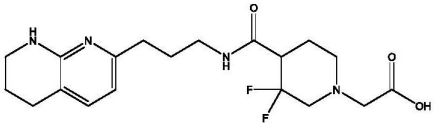
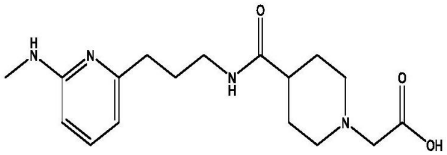
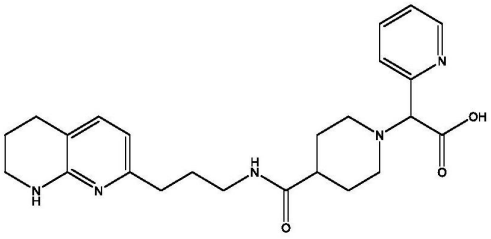
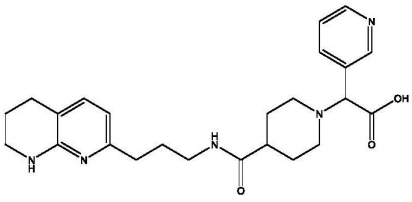
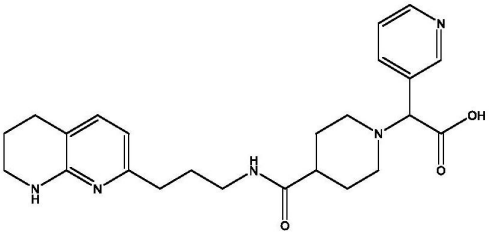
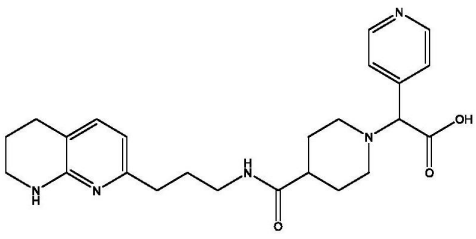
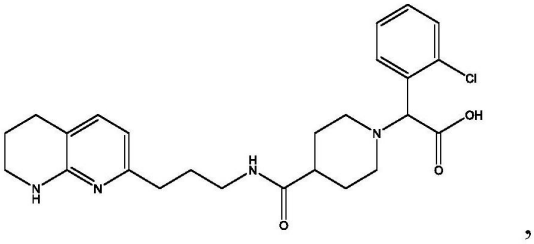
,

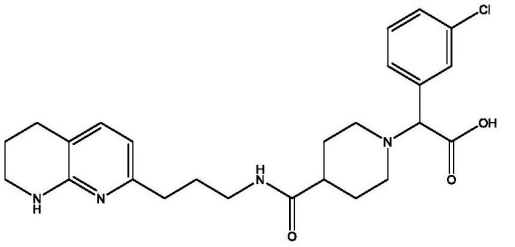
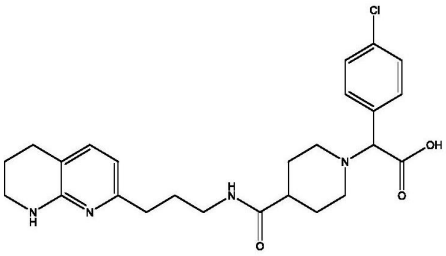
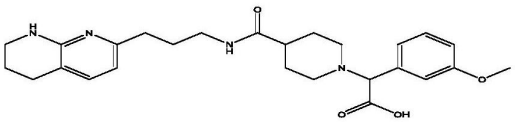
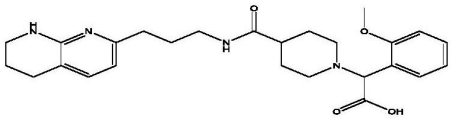
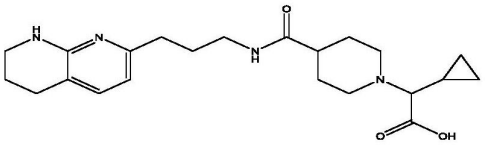
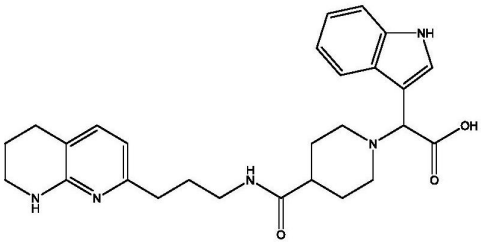
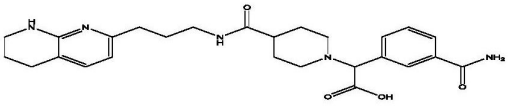
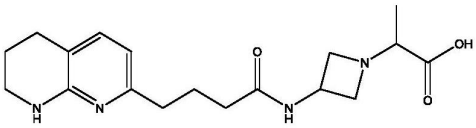
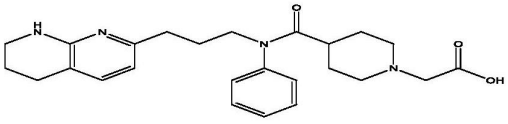
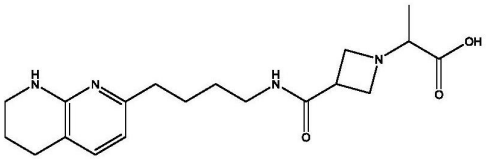
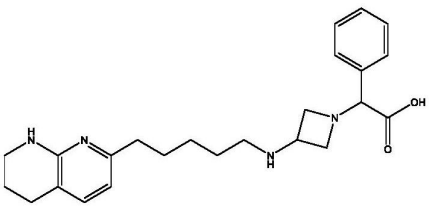
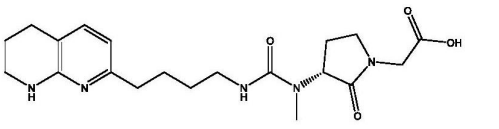

H
N
N
H
N
O
N
N
O
OH

,

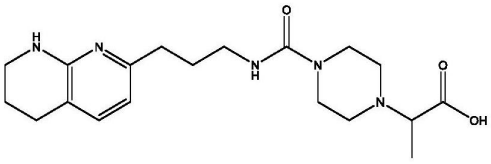

N
H
N
O
H
N
N
O
OH

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

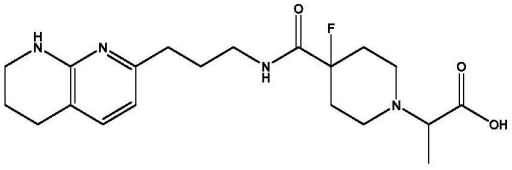
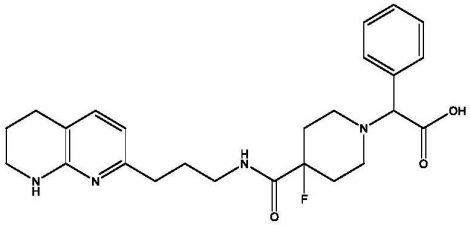
,

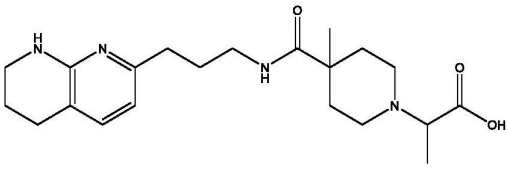
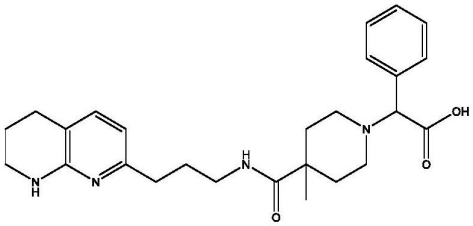
,

,

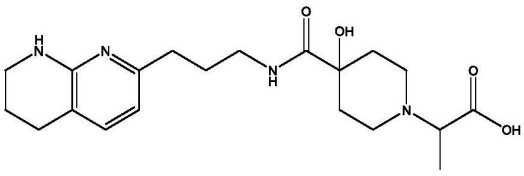
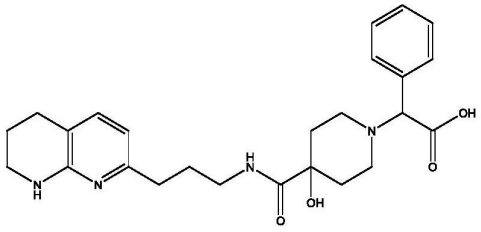
,

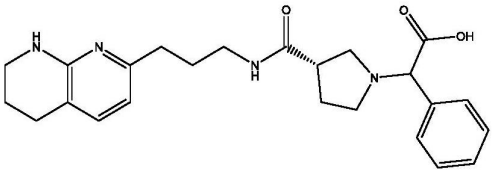
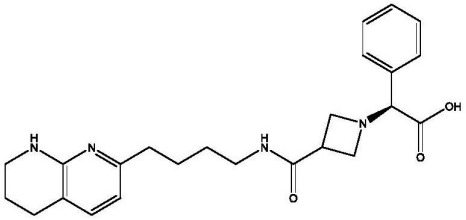
,

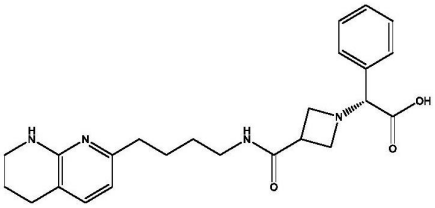
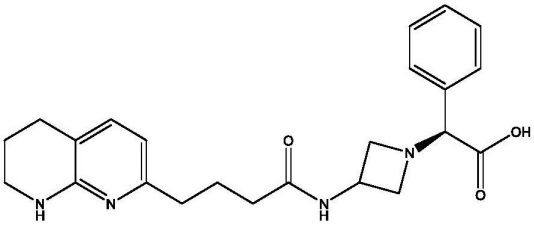
,

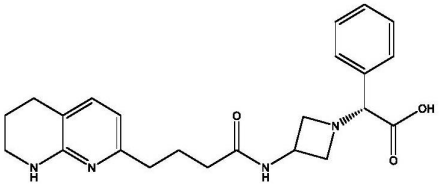
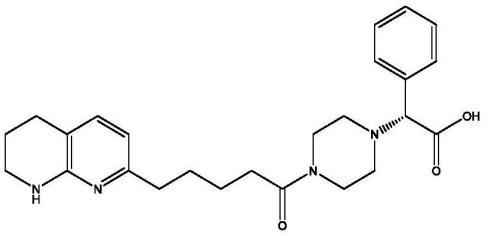

,

,

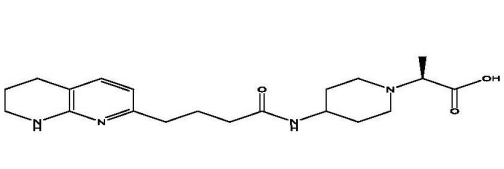

,

,


,

,

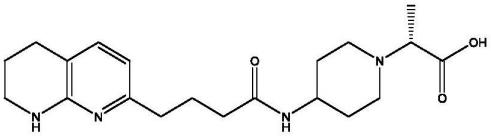

,

,

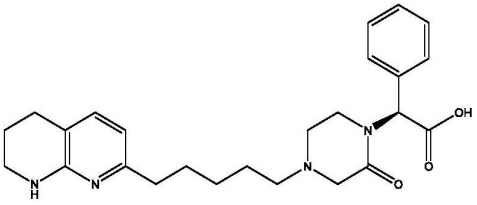
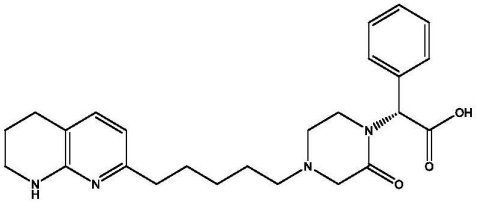
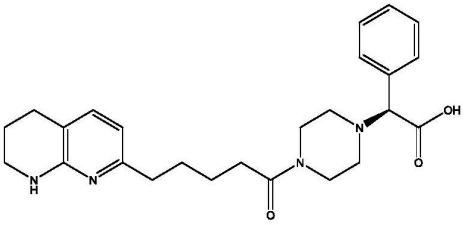
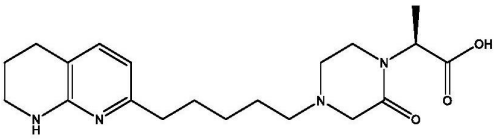
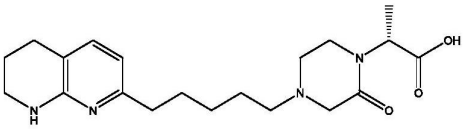
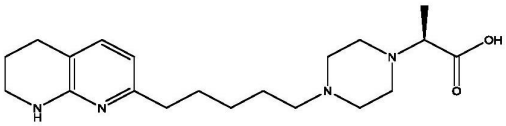
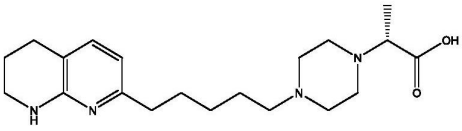
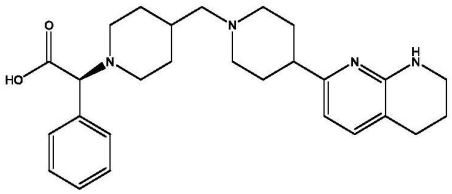
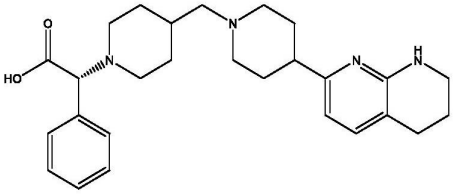
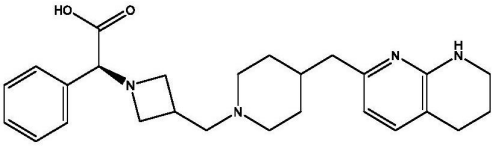
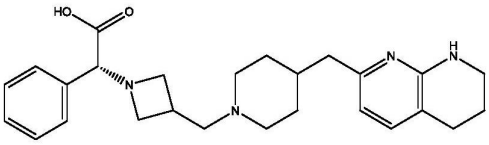
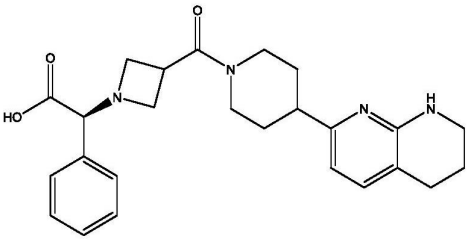
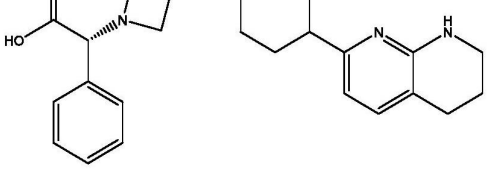

,

,


,

,

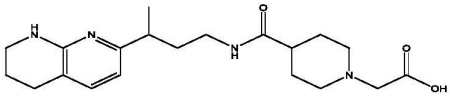

,

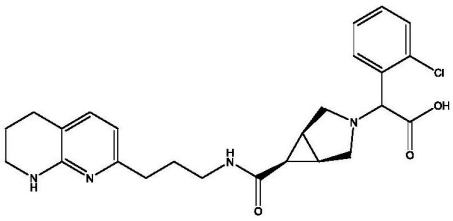
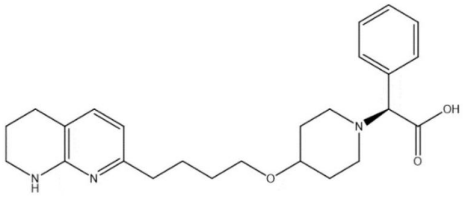
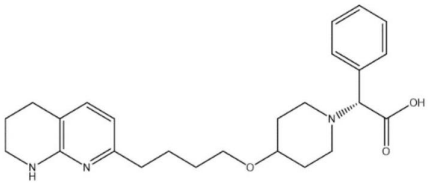
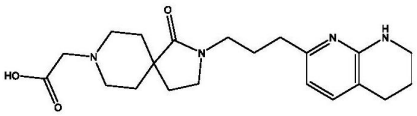
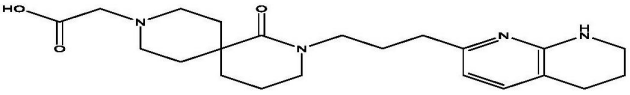
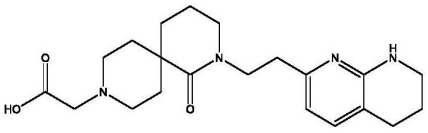
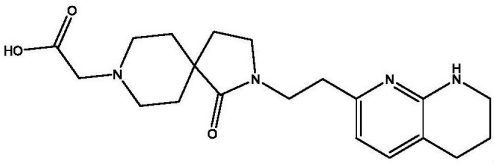
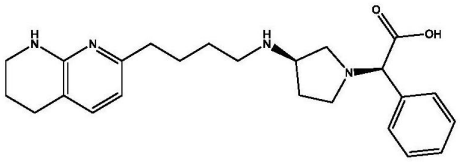
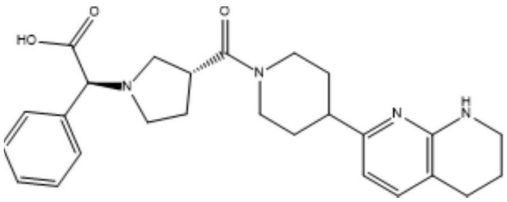
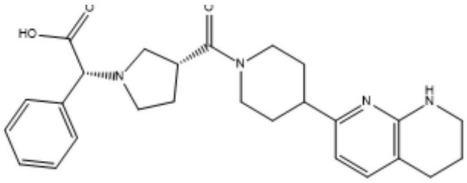
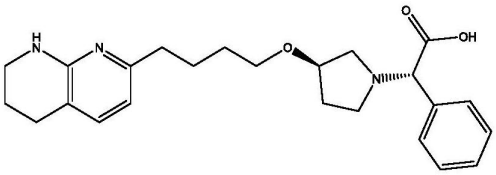
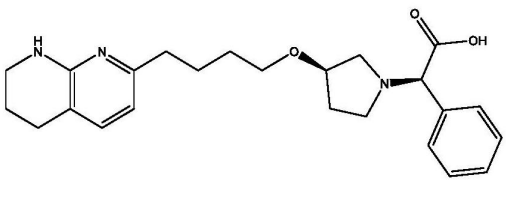
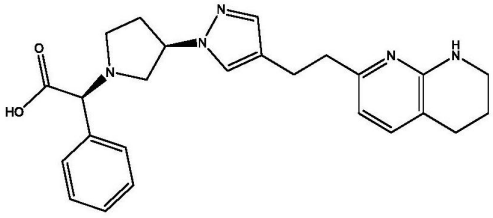
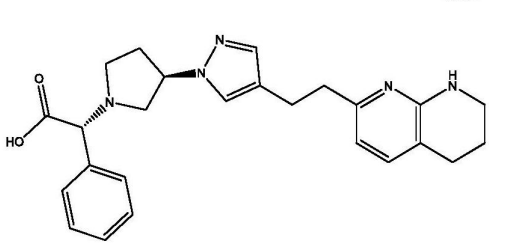
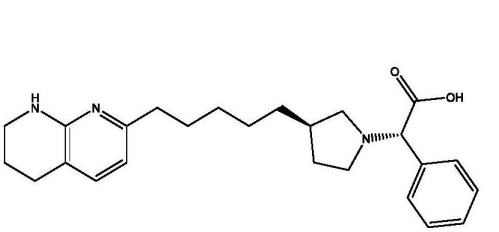
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

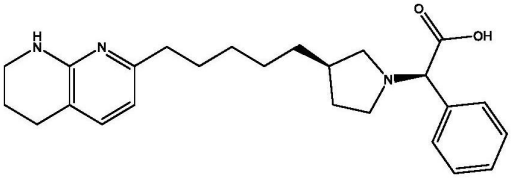
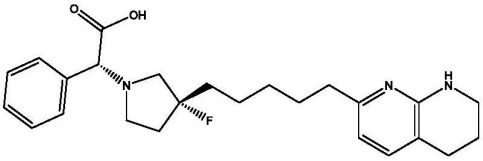
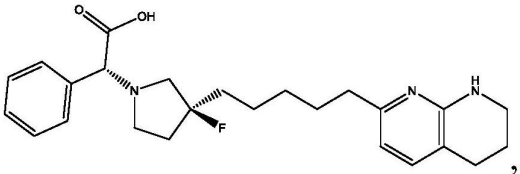
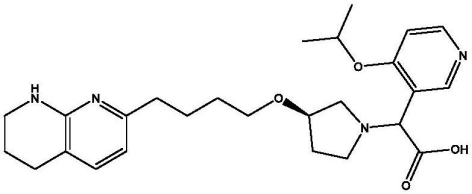
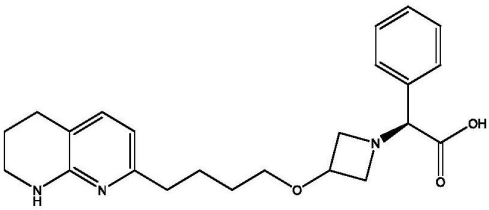
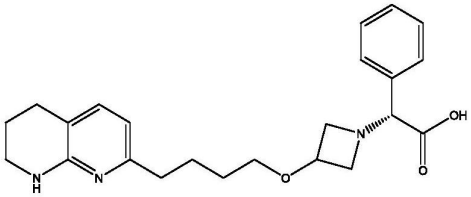
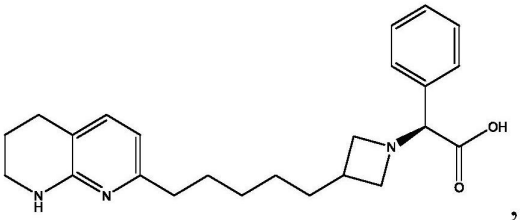
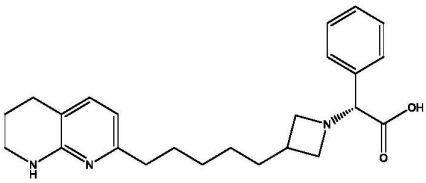
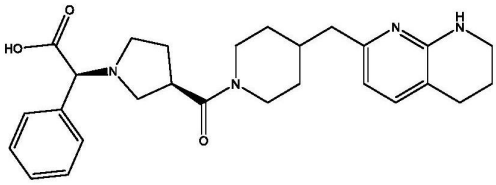
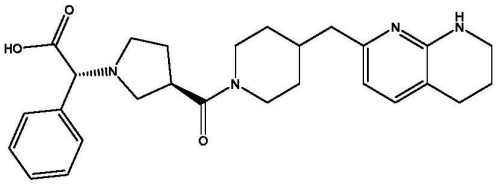
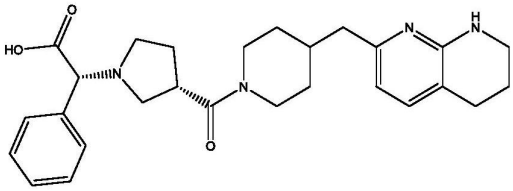
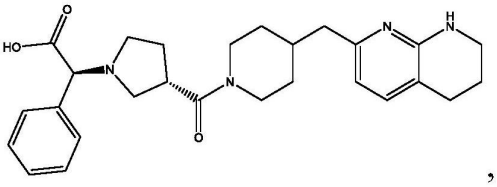
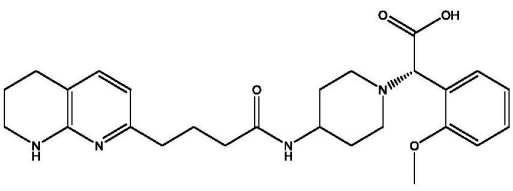
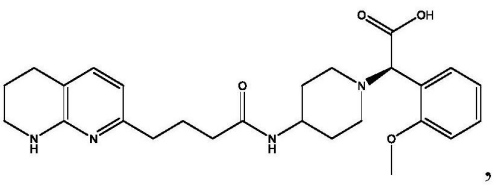
,

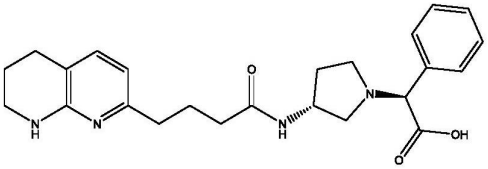
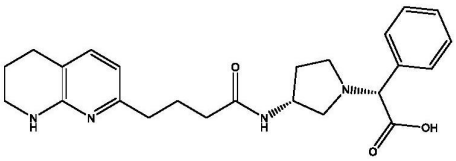
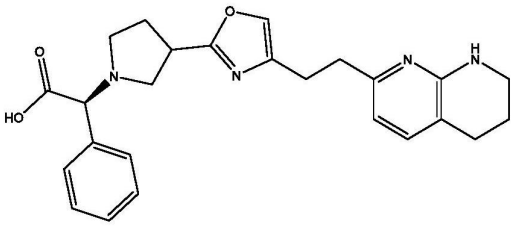
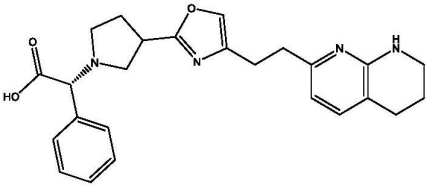
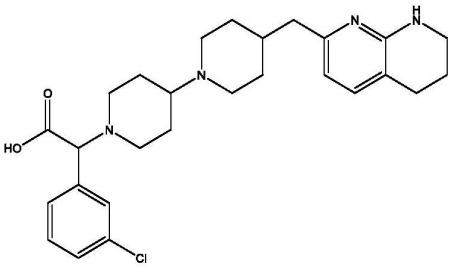
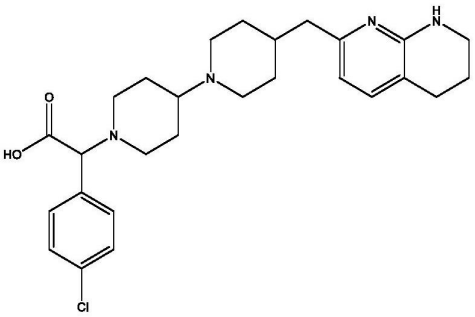
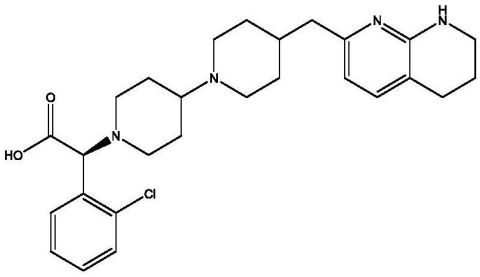
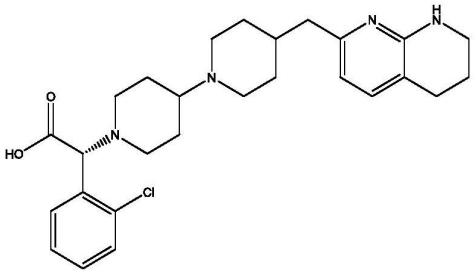
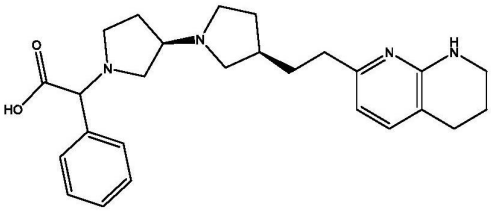
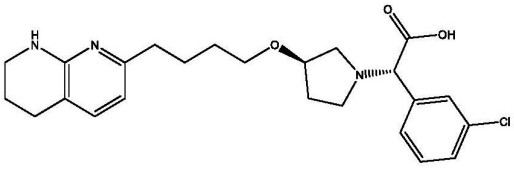
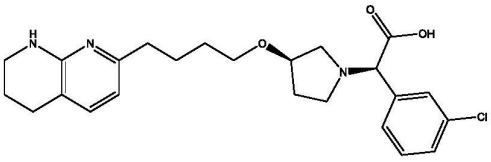
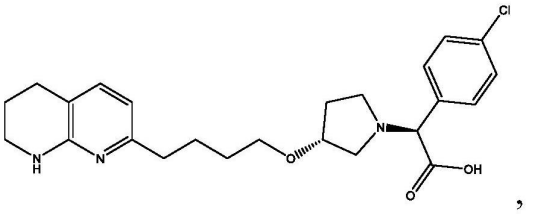
,

,

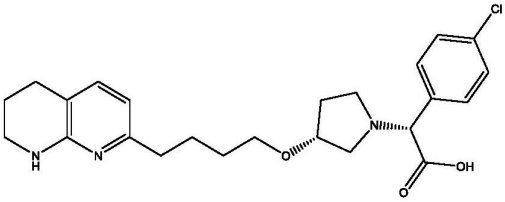
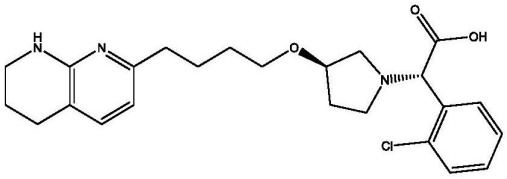
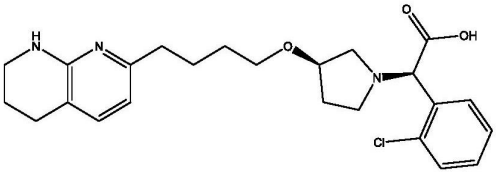
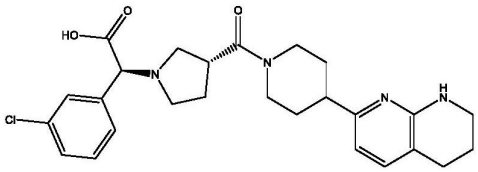
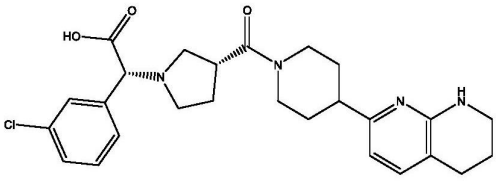
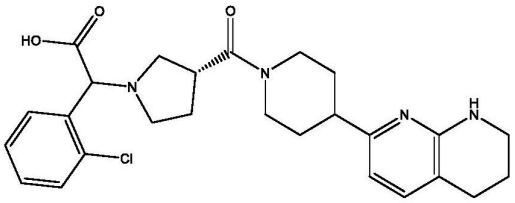
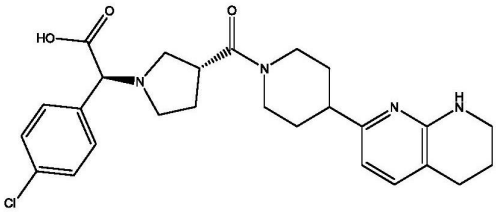
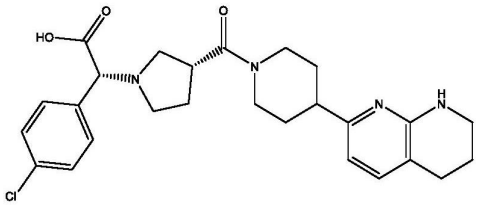
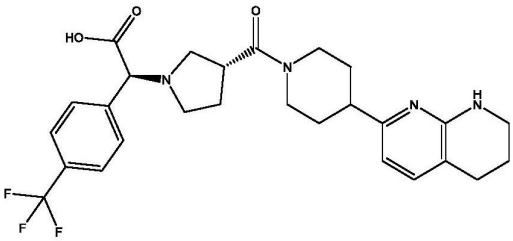
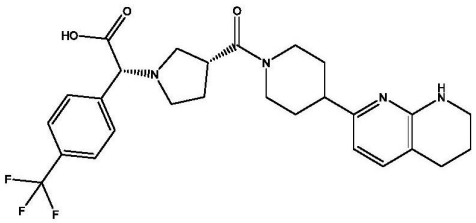
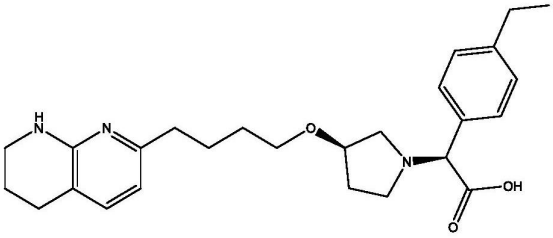
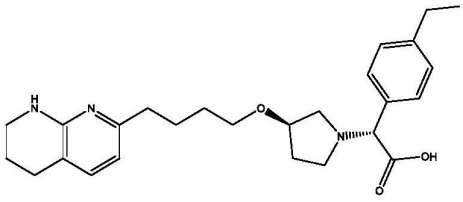
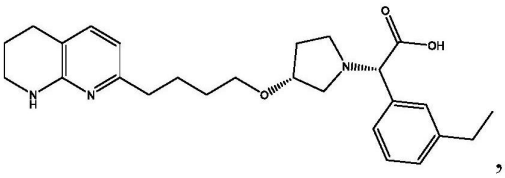

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

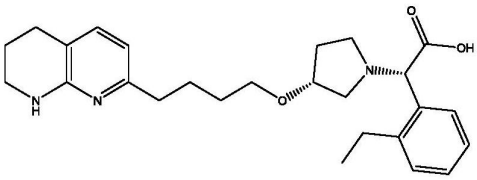
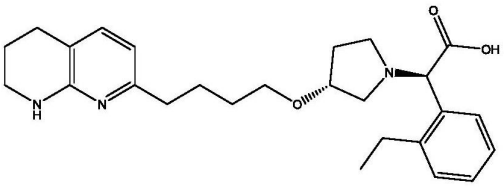
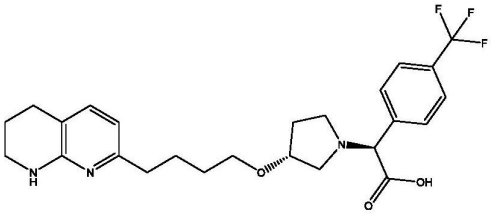
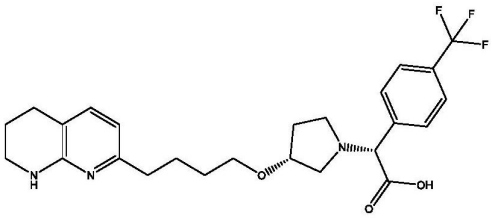
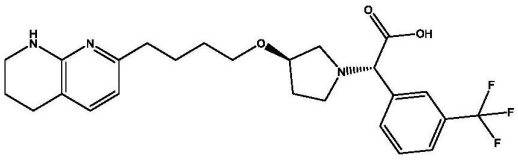
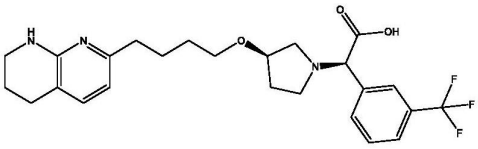
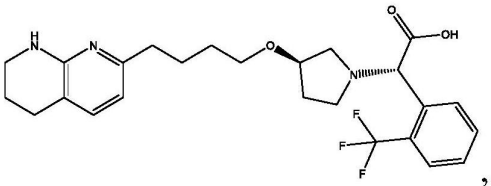
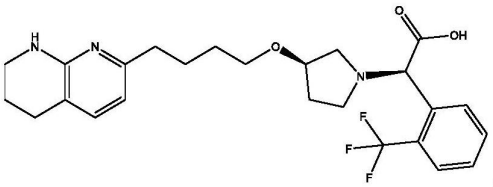
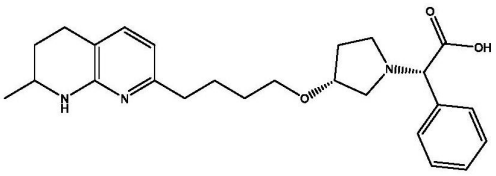
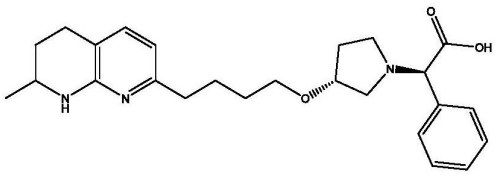
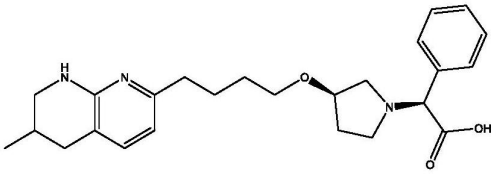
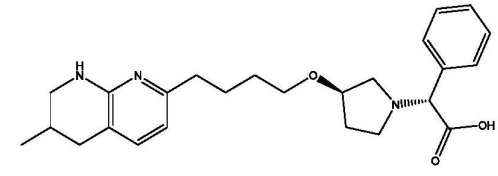
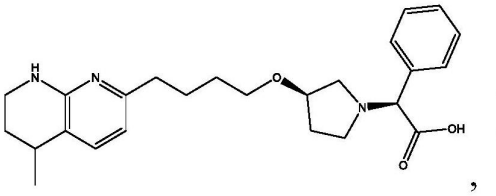
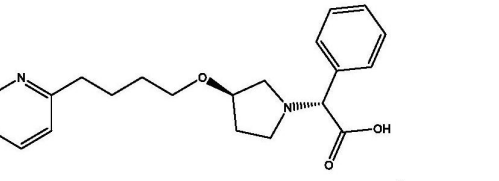
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

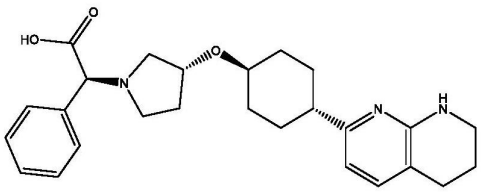
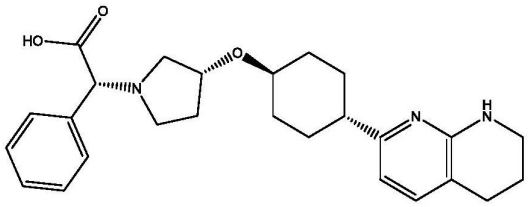
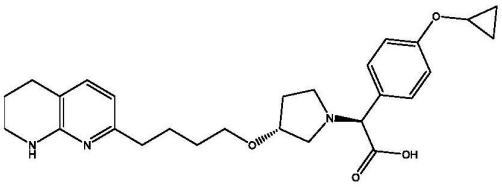
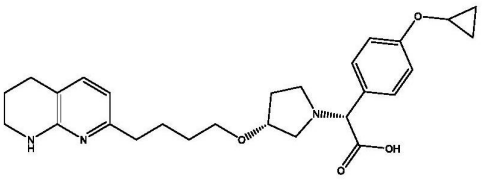
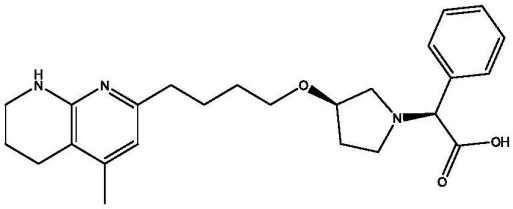
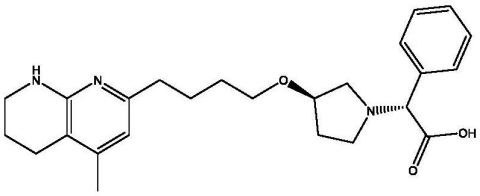
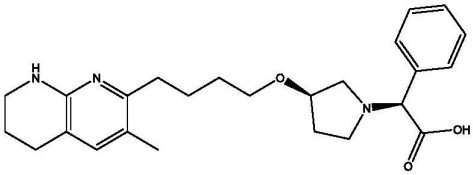
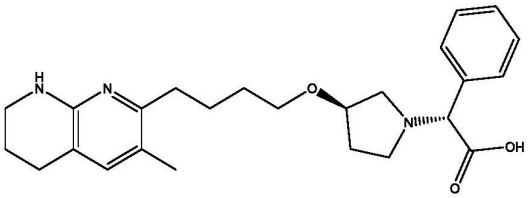
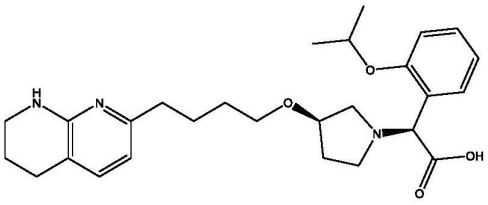
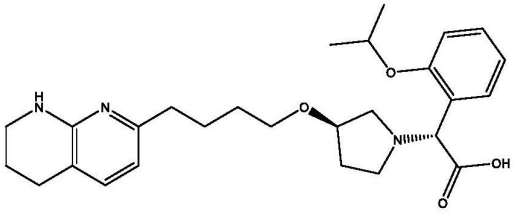

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

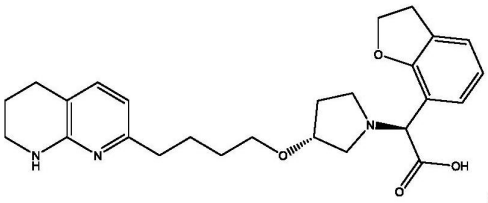
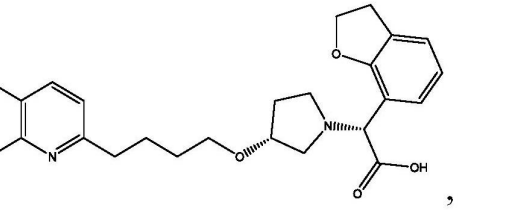

,

,

,

,

,

,

,

,

,

,

,

,

,

,

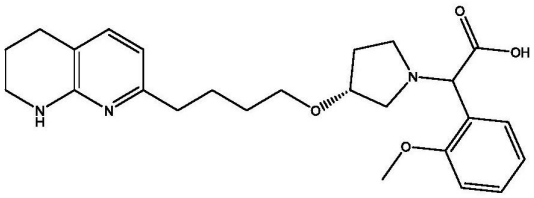
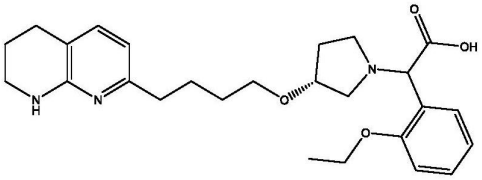
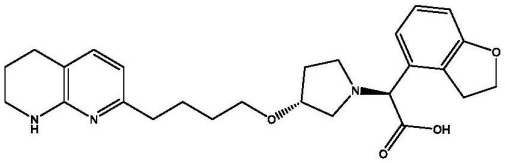
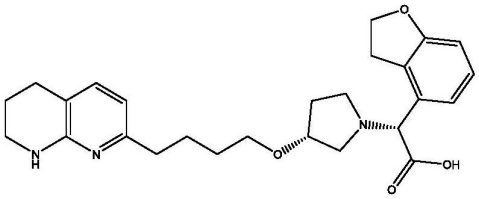
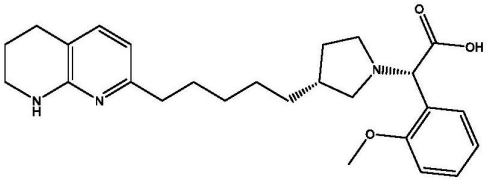
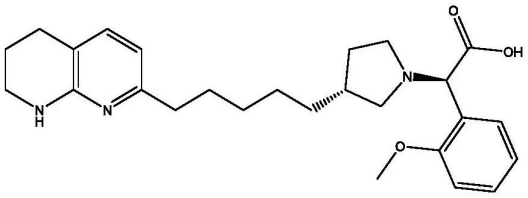
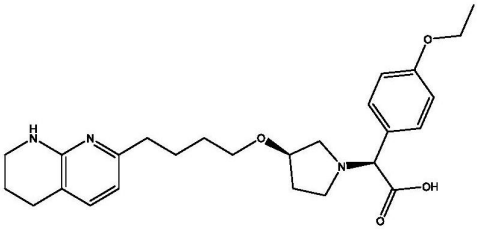
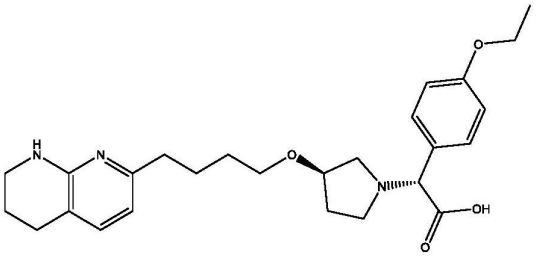
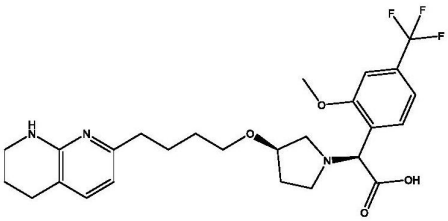
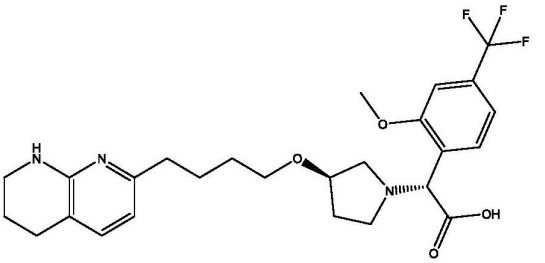
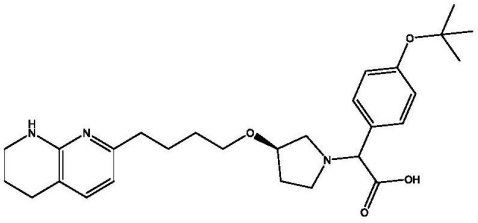
,

,

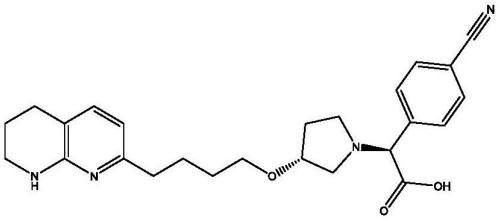
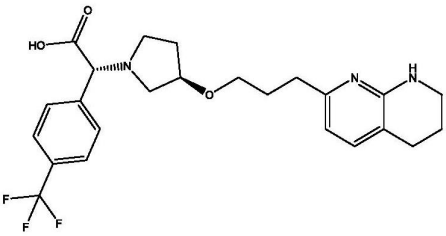
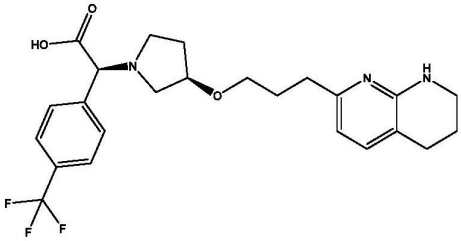
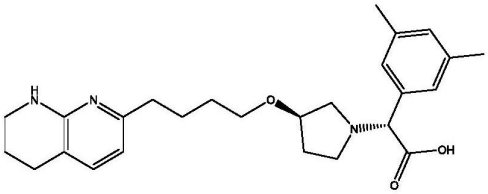
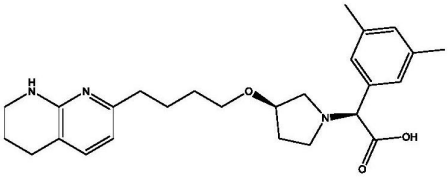
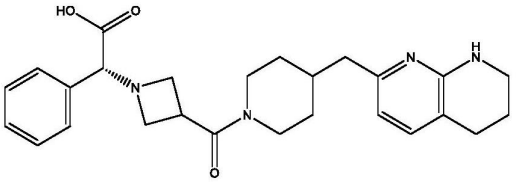
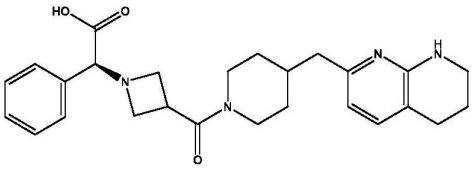
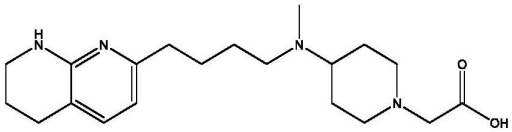
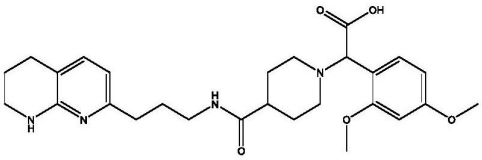
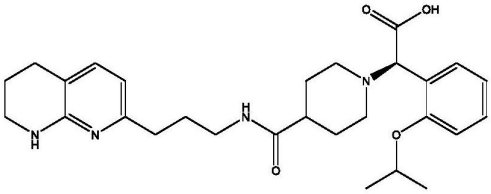
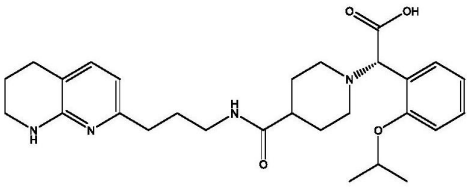
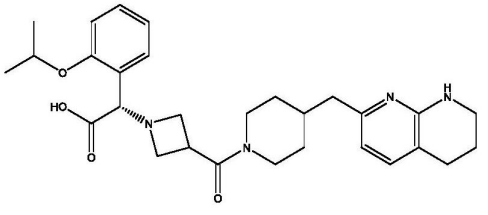

,

,

,

,

,

,

,

,

,

,

,

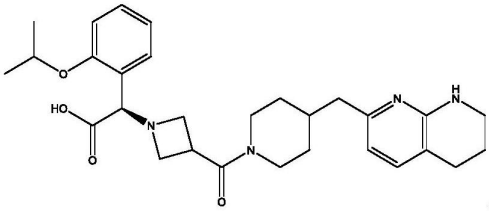
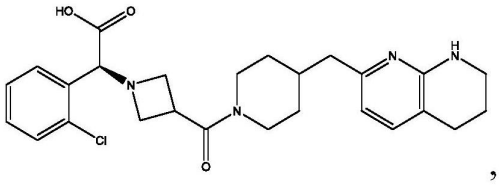
,

,

,

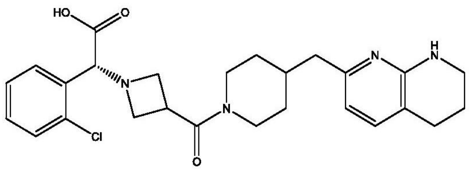

,

,

,

,

,

,

,

,

,

,

,

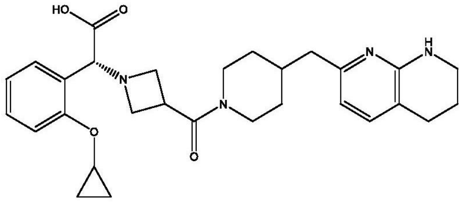
,

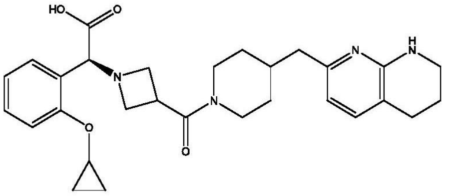

,

,

,

,

,

,

,

,

,

,

,

,

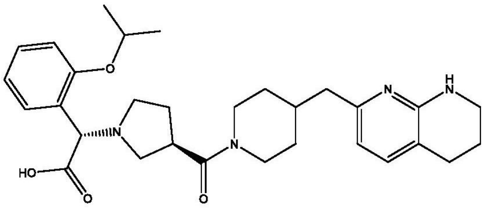
,

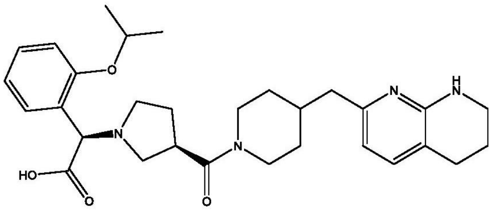
,

,

,

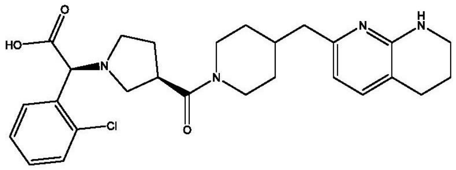

HO
O
N
Cl
O
N
N
N
H
,

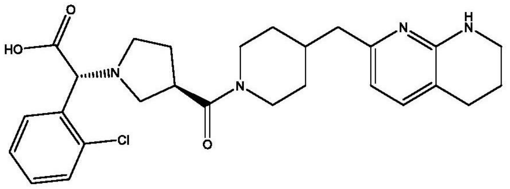

HO
O
N
O
O
N
N
N
H
,

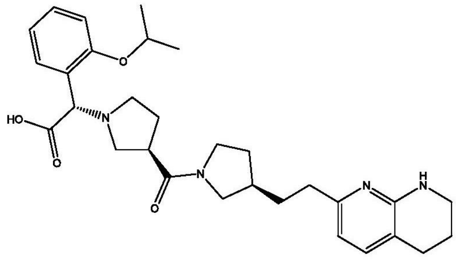

HO
O
N
O
O
N
N
N
H
,

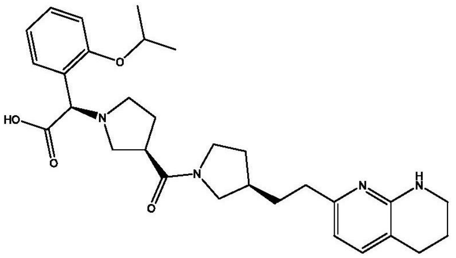

O
N
HO
O
O
N
N
N
H
,

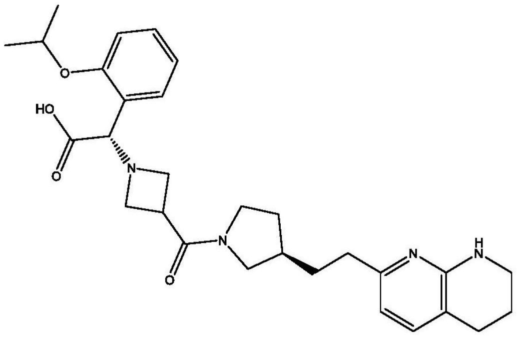

O
N
HO
O
O
N
N
N
H
,

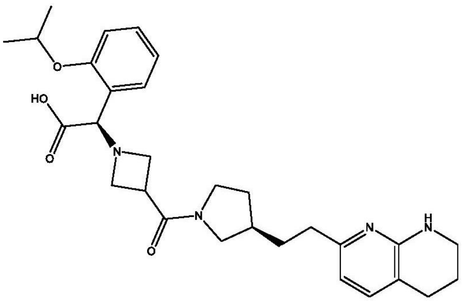

O
HO
N
Cl
O
N
N
N
H
,

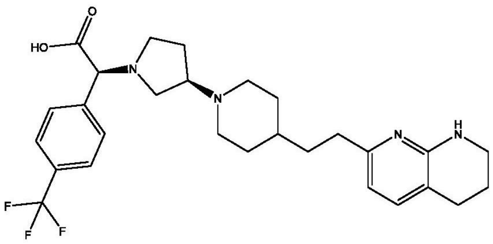

O
HO
N
Cl
O
N
N
N
H
,

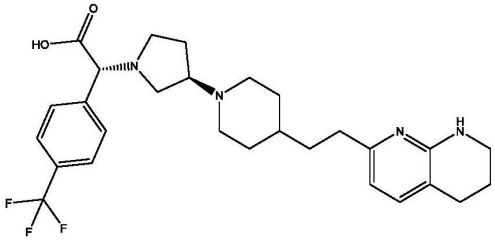
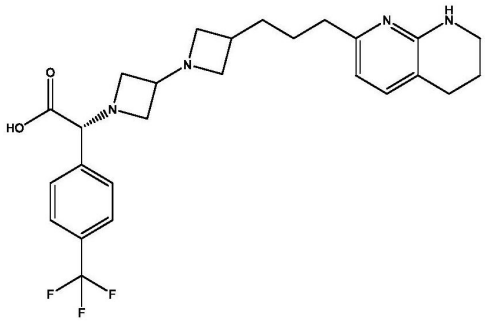
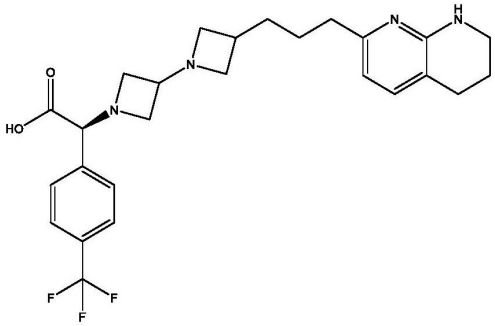
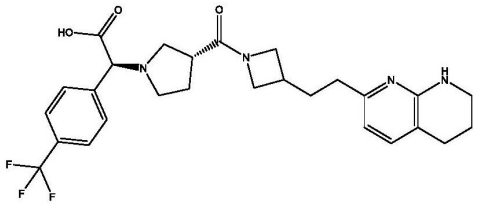
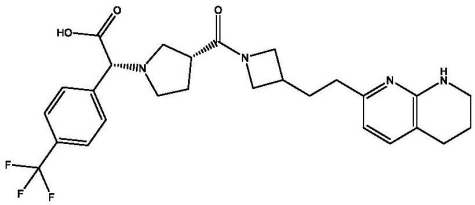
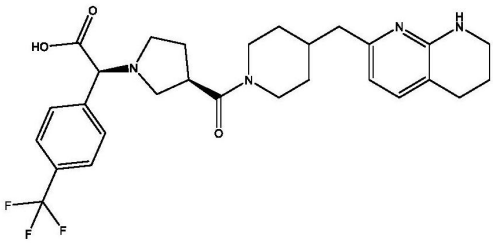
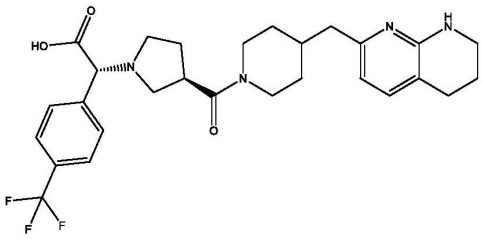
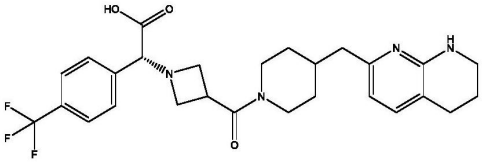
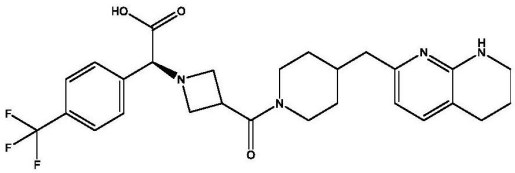
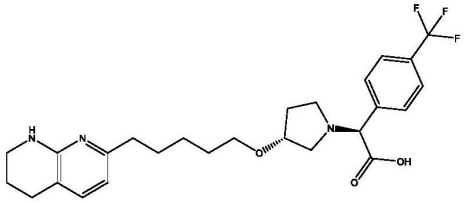

O
HO
N
O
O
N
N
N
H
,


O
HO
N
O
O
N
N
N
H
,


O
HO
O
N
O
N
N
N
H
,


O
HO
O
N
O
N
N
N
H
,


O
HO
N
N
F
F
F
N
N
H
,

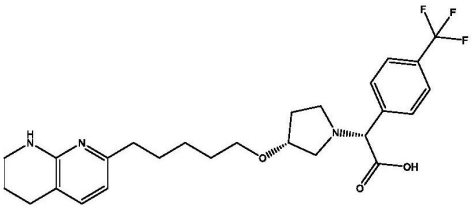
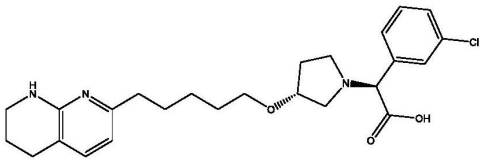
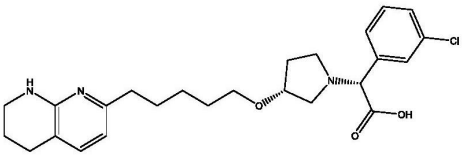
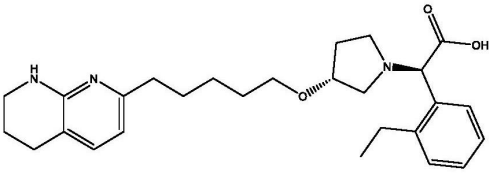
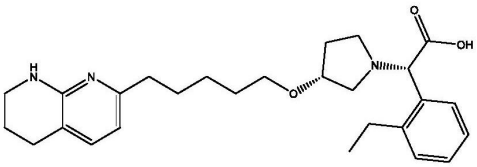
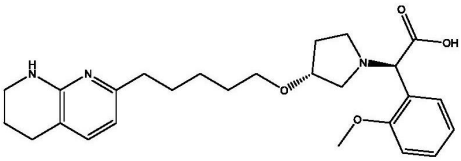
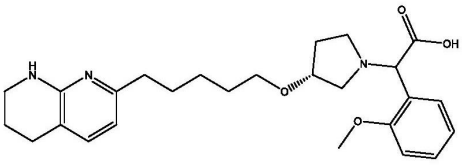
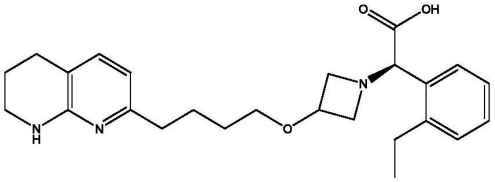
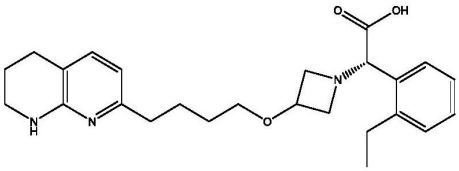
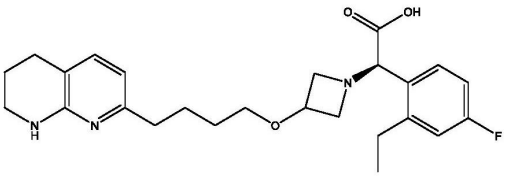
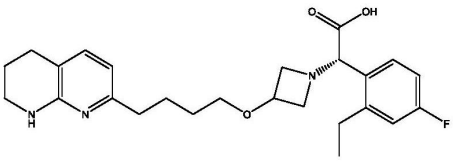
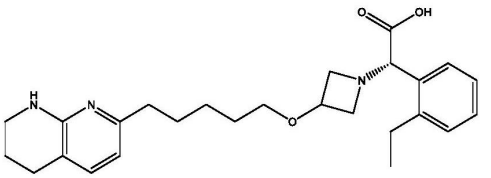
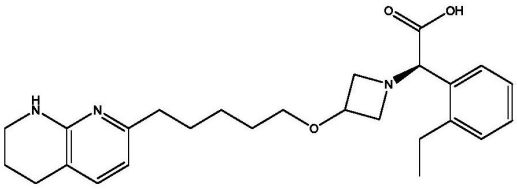

,

,

,

,

,

,

,

,

,

,

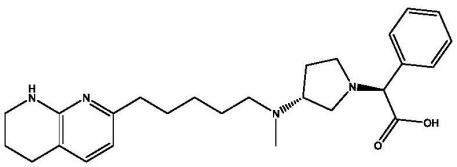
,

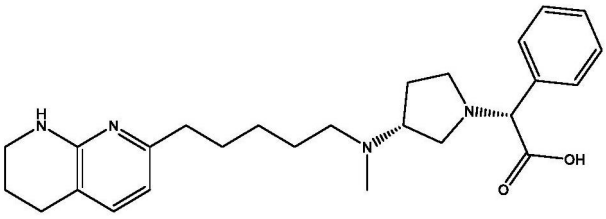
,

,

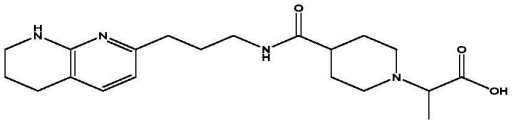
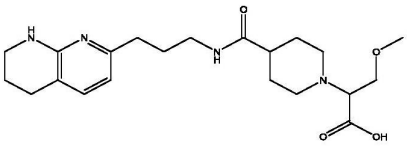
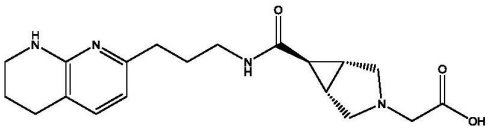
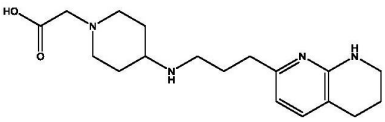
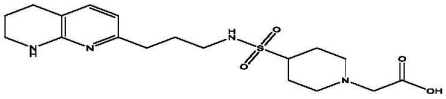
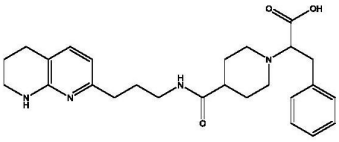
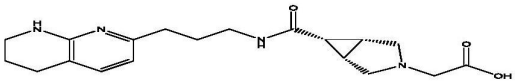
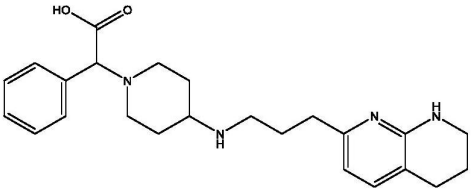
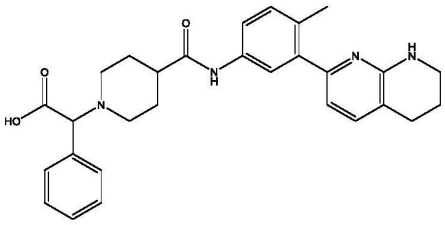
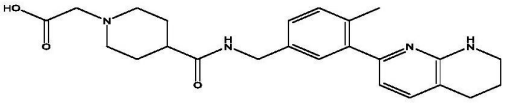
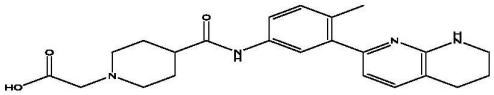
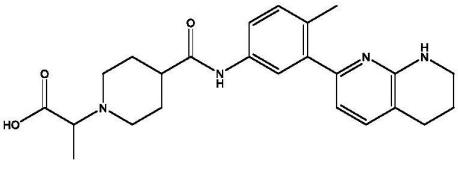
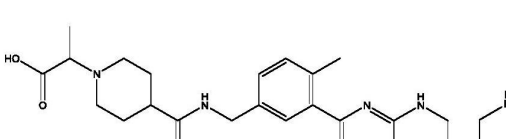
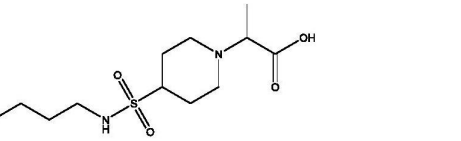
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

和

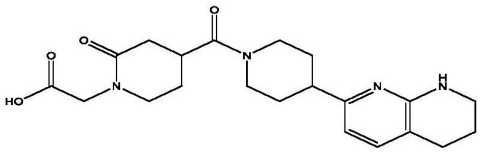
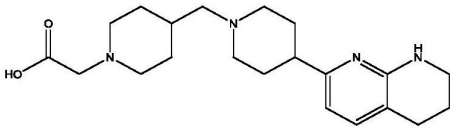
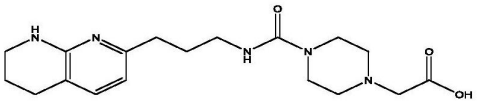
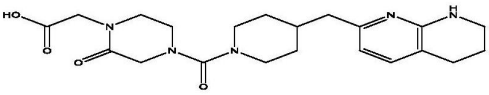
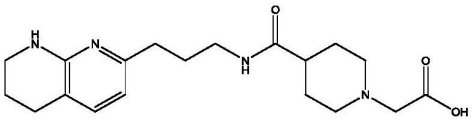
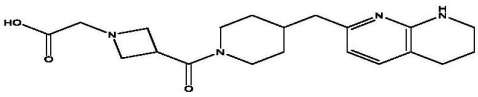
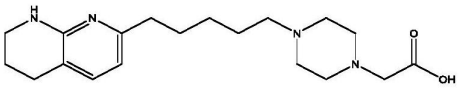
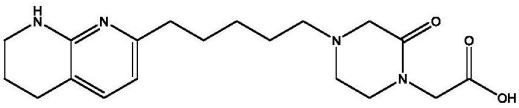
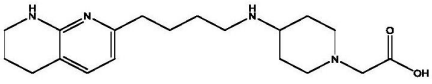
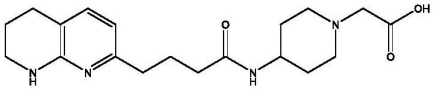
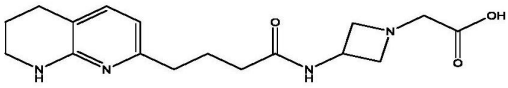
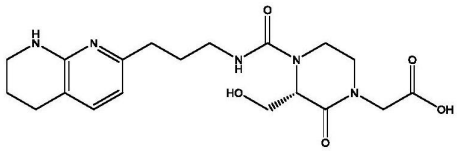
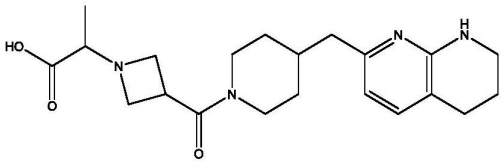
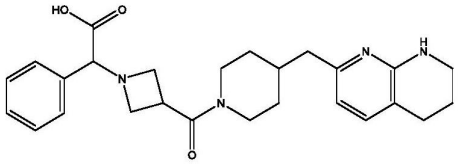

,
或其药学上可接受的盐。

2.根据权利要求1所述的化合物,其中所述化合物选自由如下组成的组:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

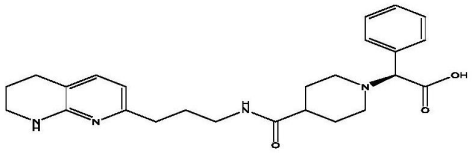
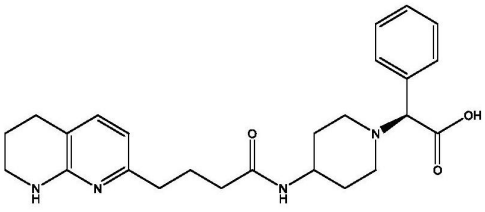
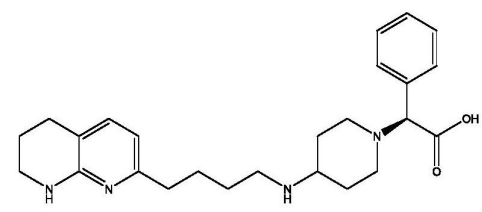
,

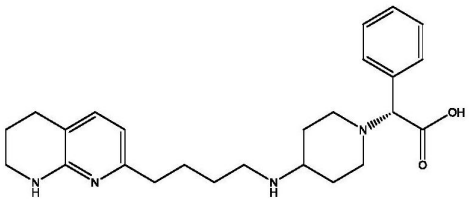
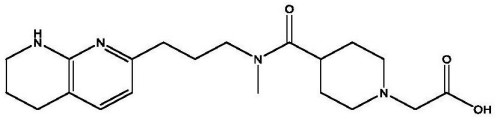
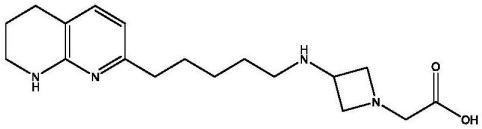
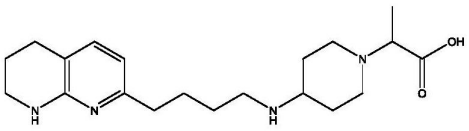
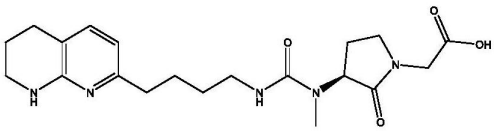
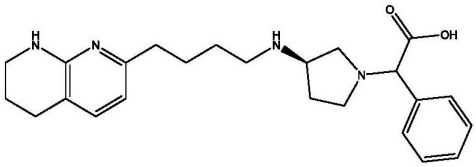
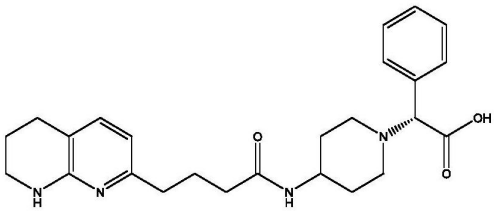
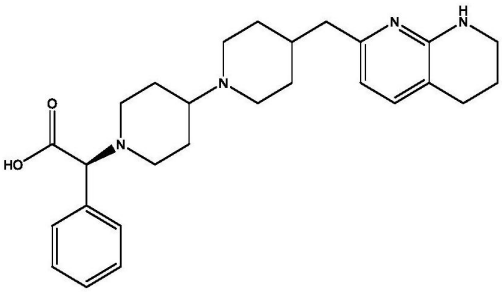
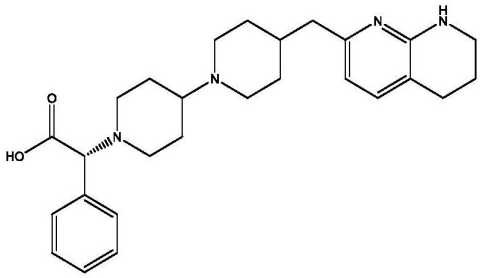
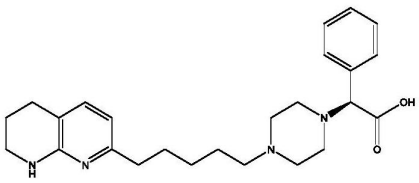
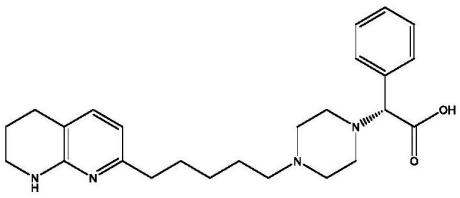
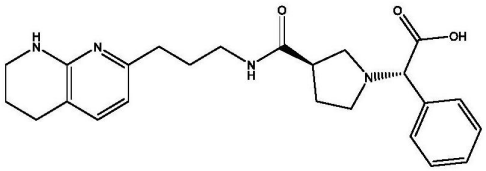
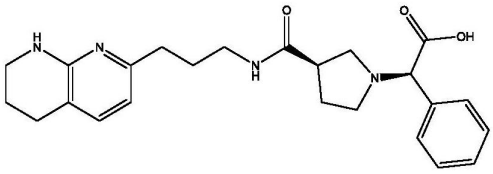
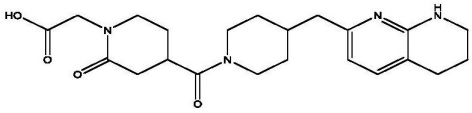
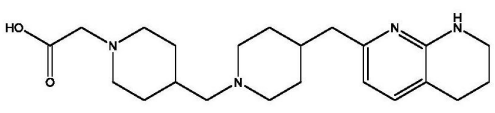
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

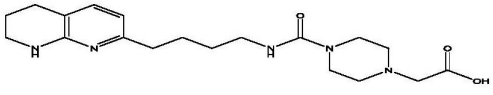
,

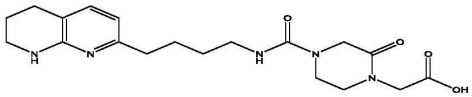
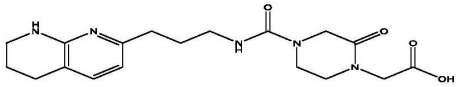
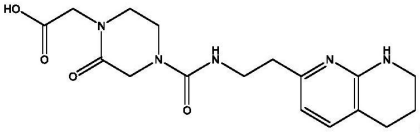
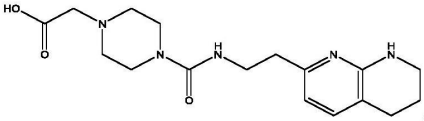
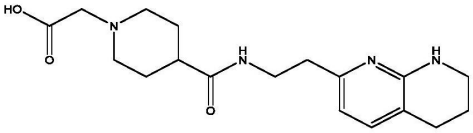
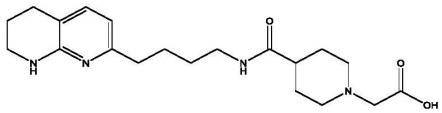
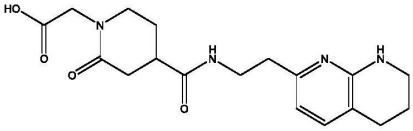
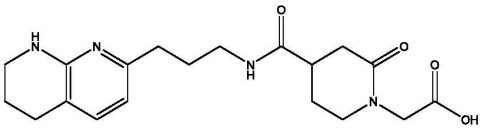
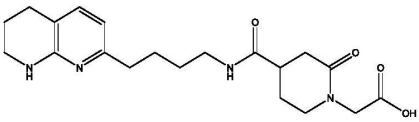
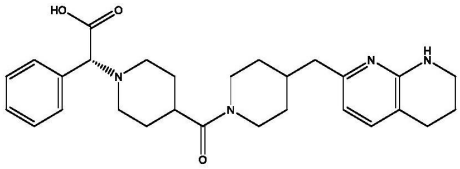
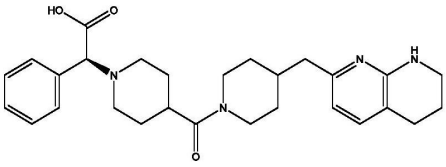
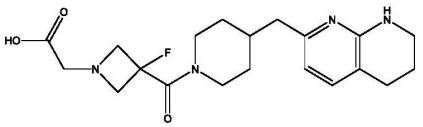
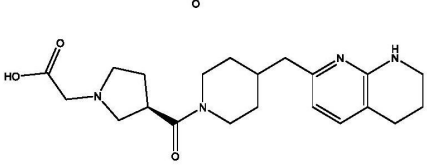
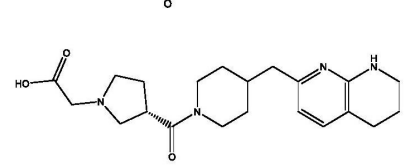
,

,

,

,

,

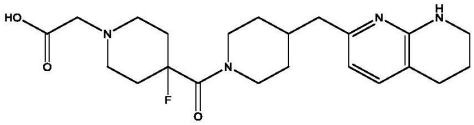
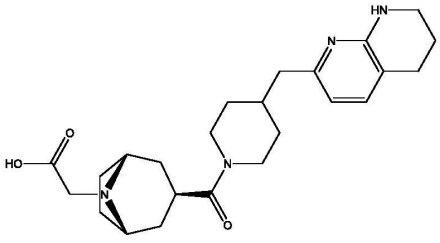
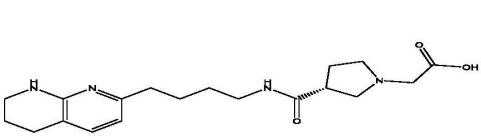
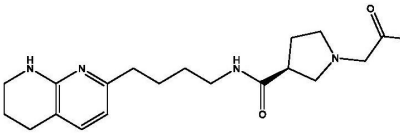

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

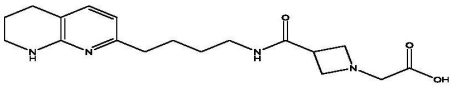
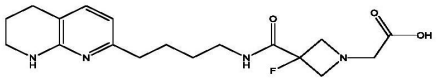
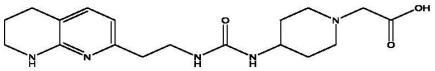
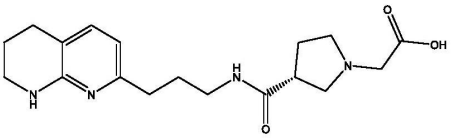
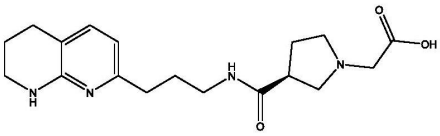
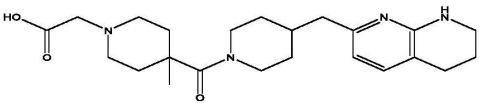
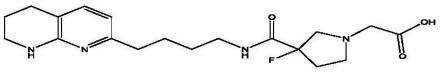
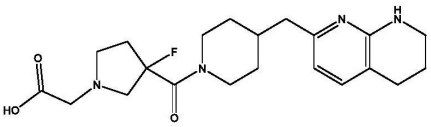
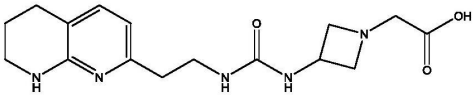
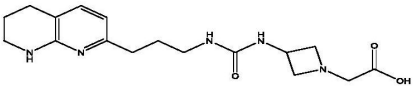
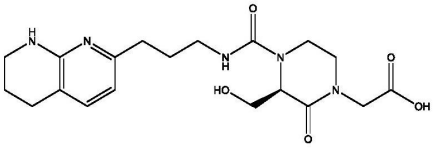
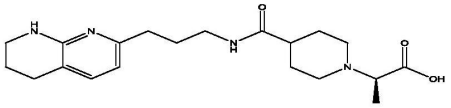
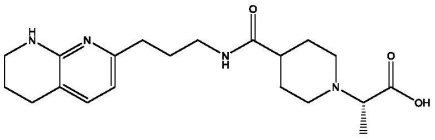
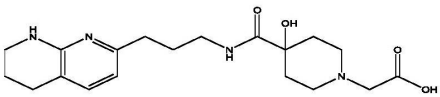
,

,

,

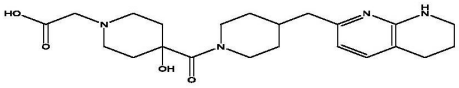
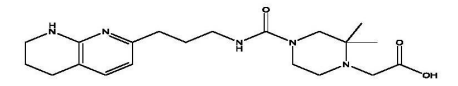
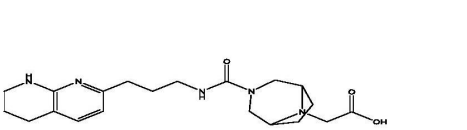
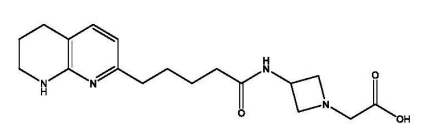

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

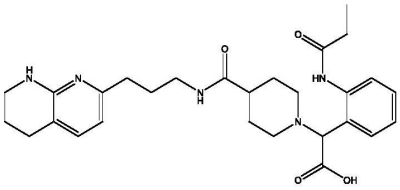
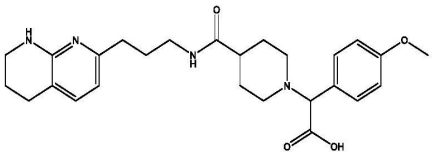
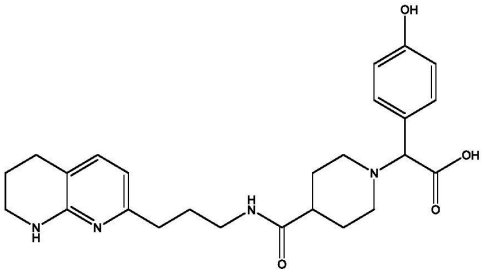
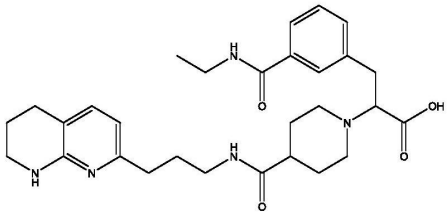
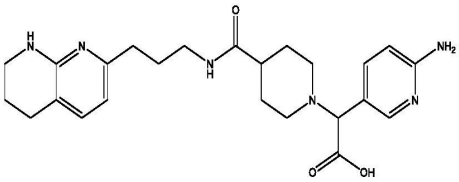
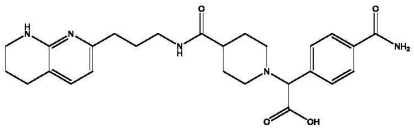
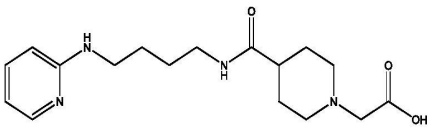
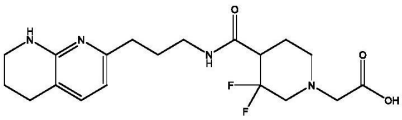
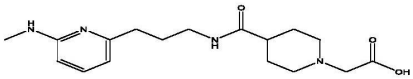
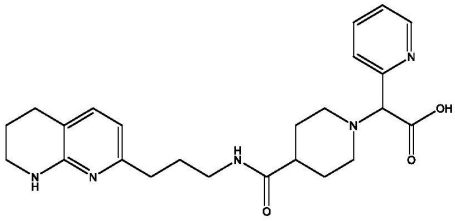
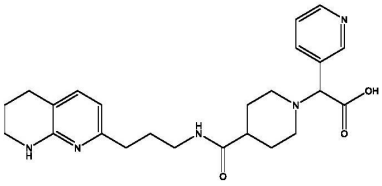
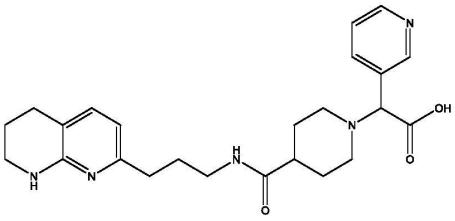
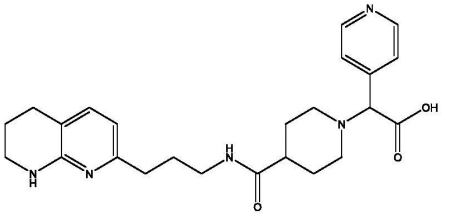
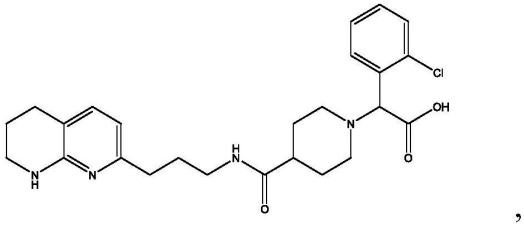
,

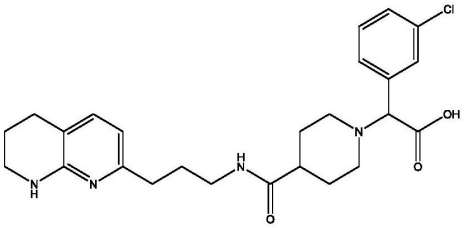
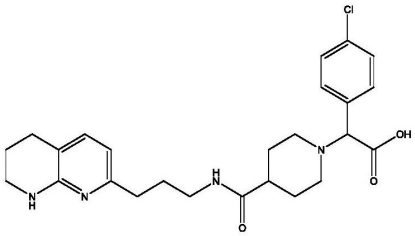
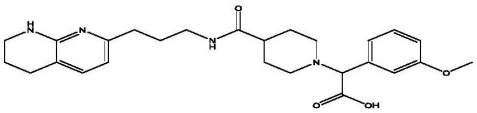
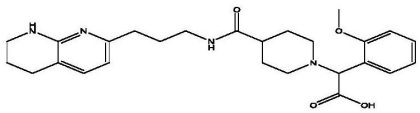
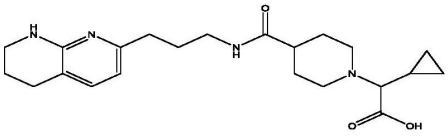
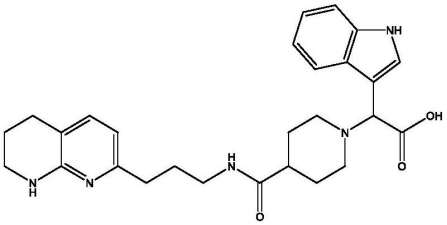
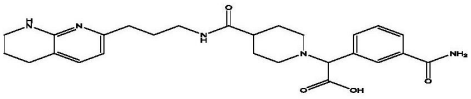
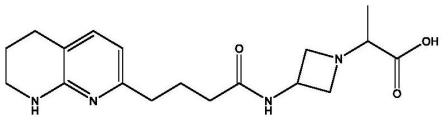
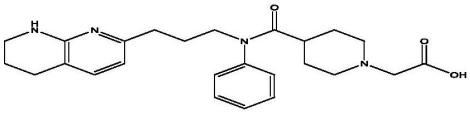
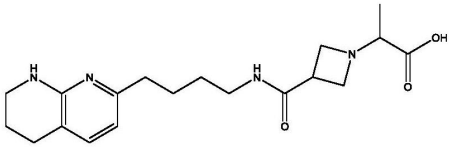
,

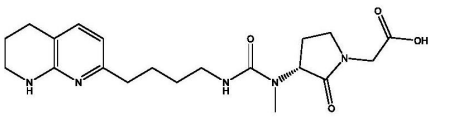
,

,

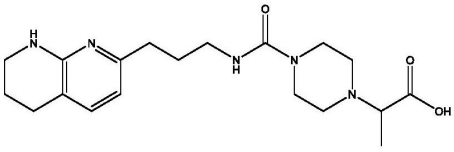
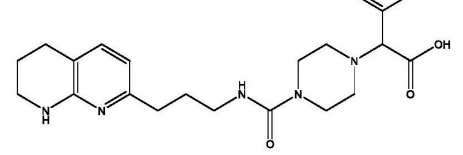
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

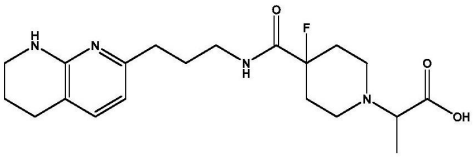
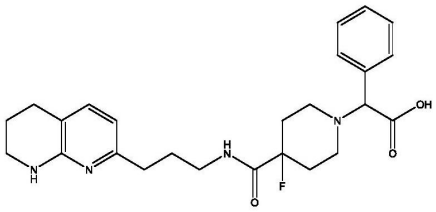
,

,

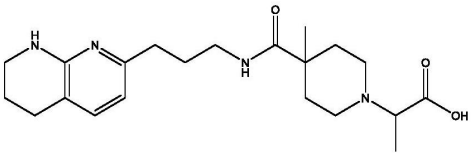
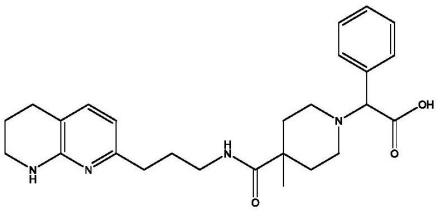
,

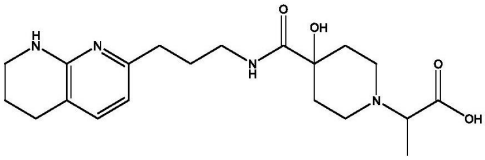
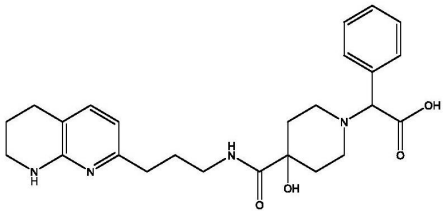
,

,

,

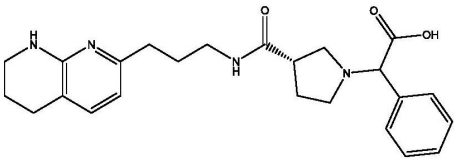
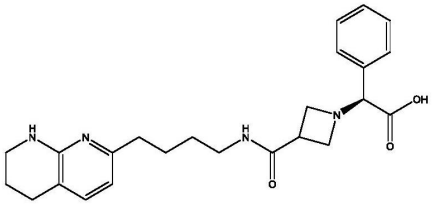
,

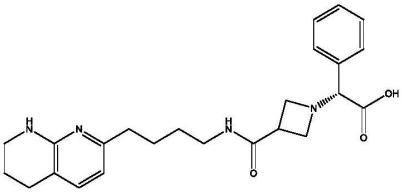
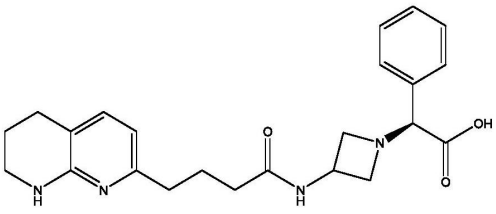
,

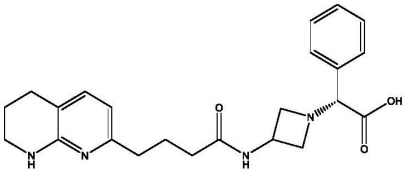
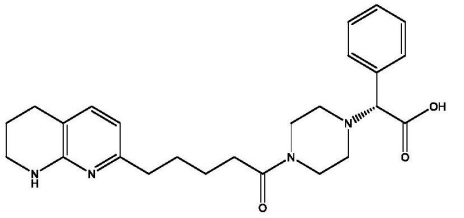

,

,

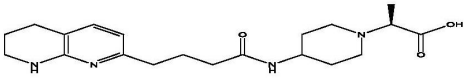

,

,

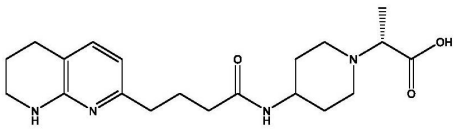

,

,

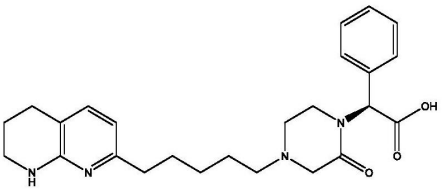
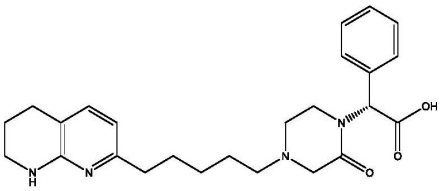
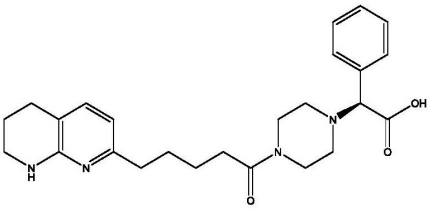
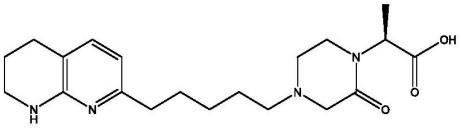
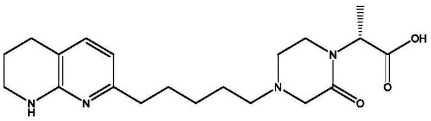
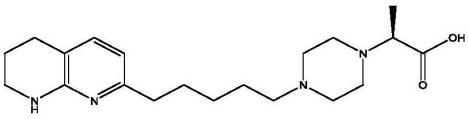
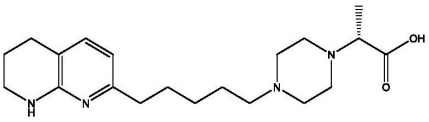
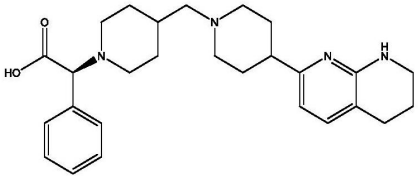
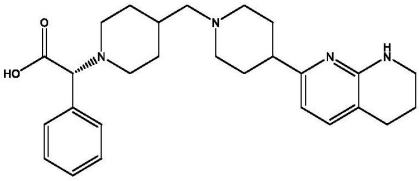
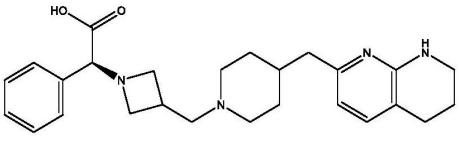
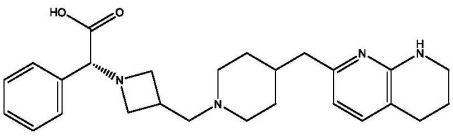
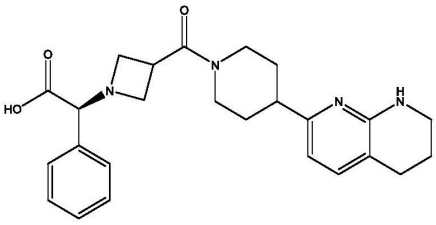
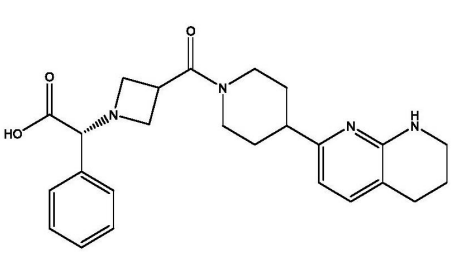
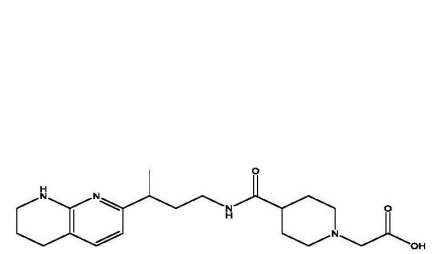

,

,


,

,


,

,

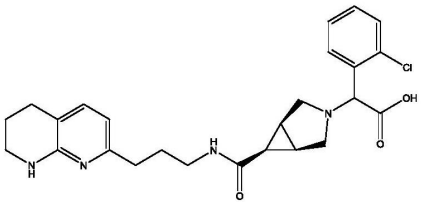
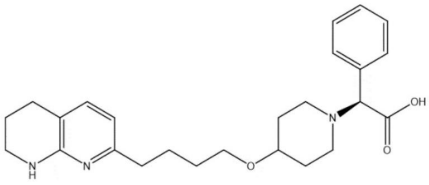
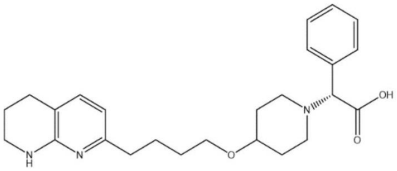
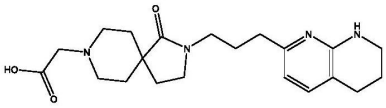
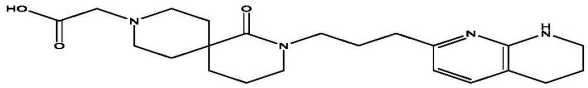
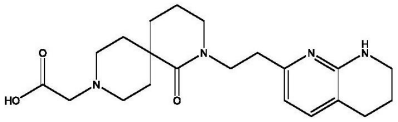
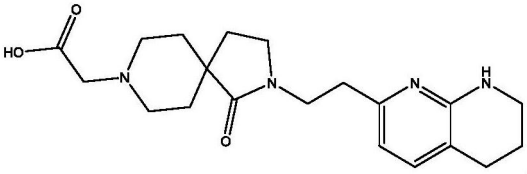
,

,


,

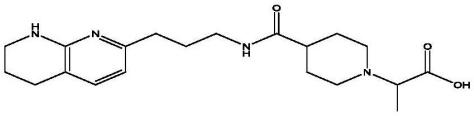
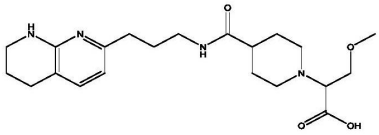
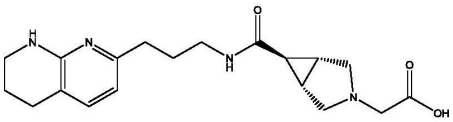
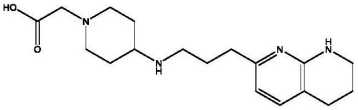
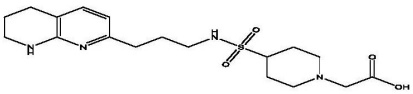
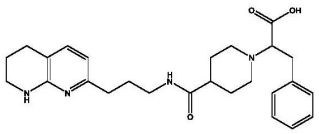
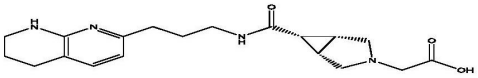
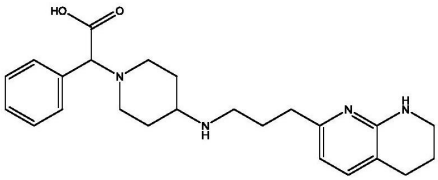

,

,

,

,

,

,

,

,

,

,

,

,

,

,

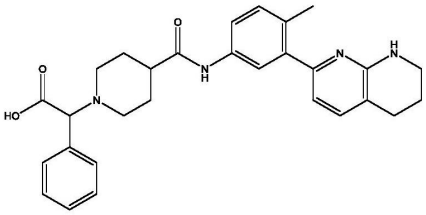
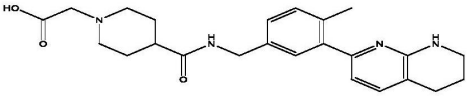
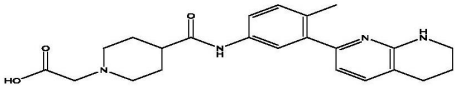
,

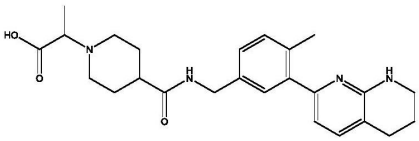
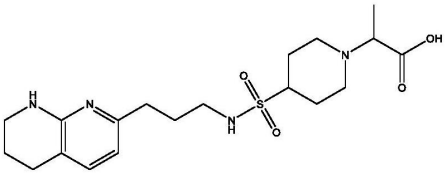
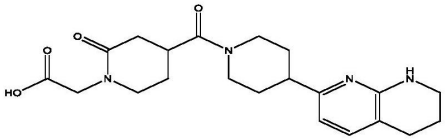
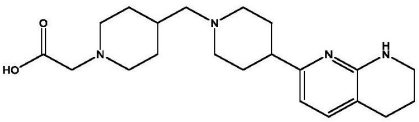
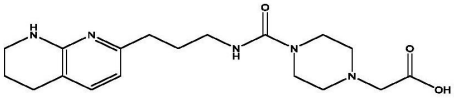
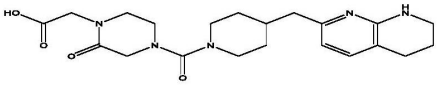
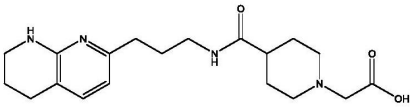
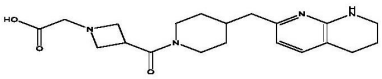
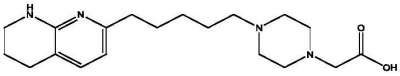
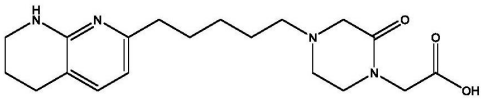
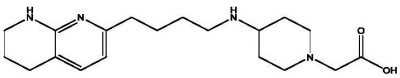
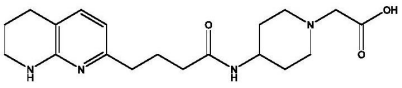
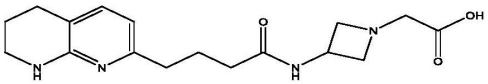
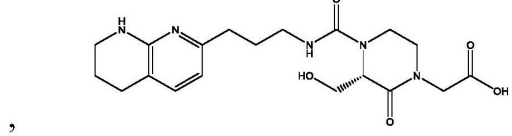
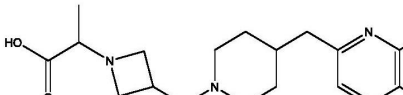
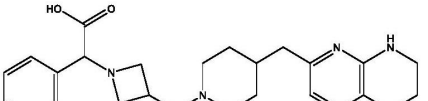
,


，

，

，

，

，

和

，或其药学上可接受的盐。

3.根据权利要求1所述的化合物，其中所述化合物选自由如下组成的组：


，

，

，

，

，

，

，

，


,

,

,

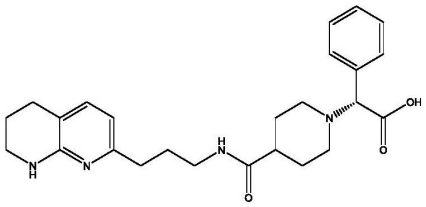
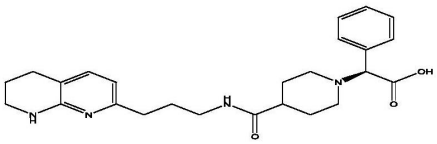
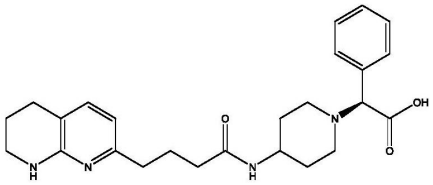
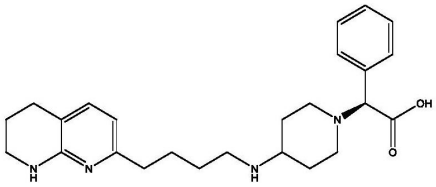
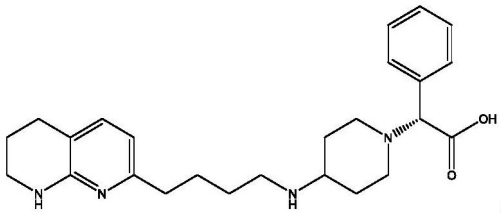
,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

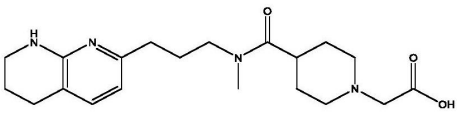
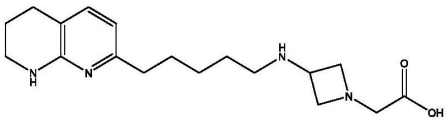
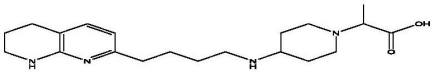
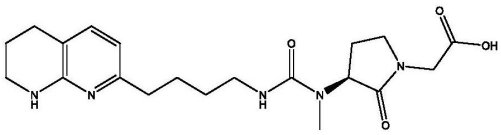
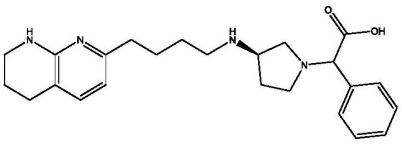
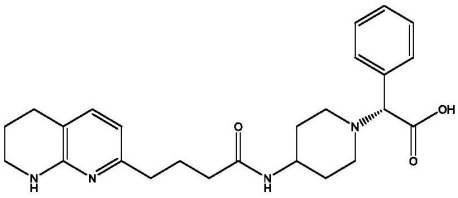
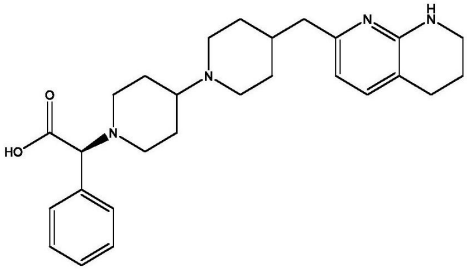
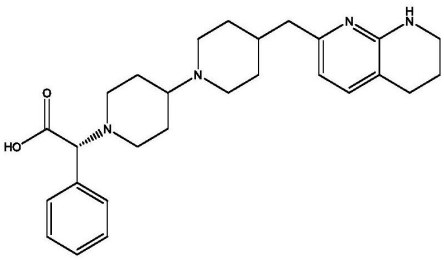
,

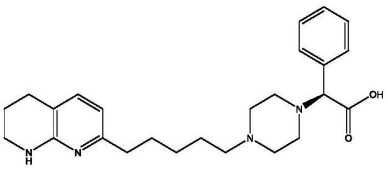
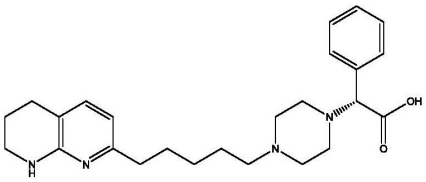
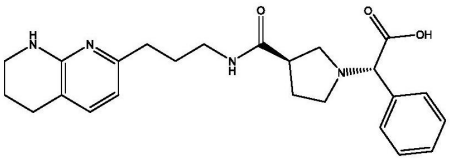
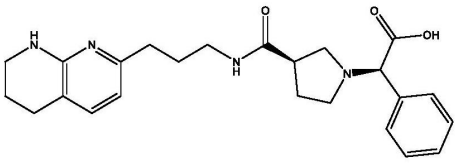
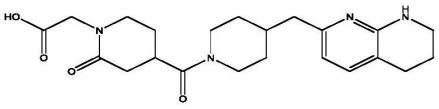
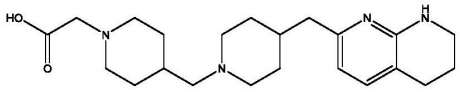
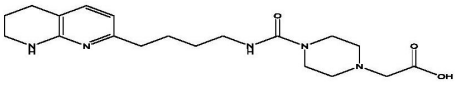
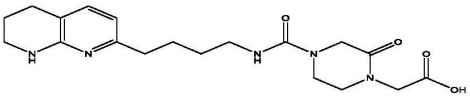
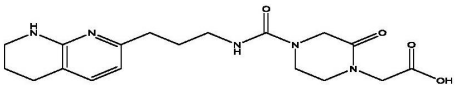
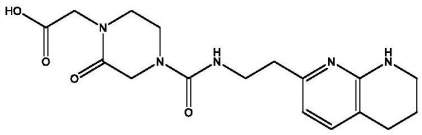
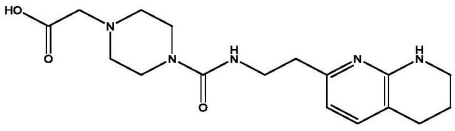
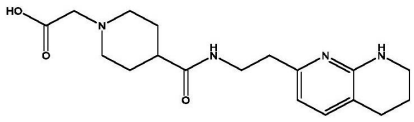
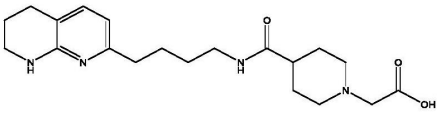
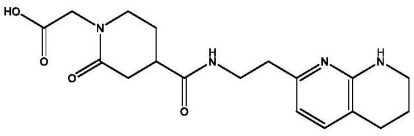
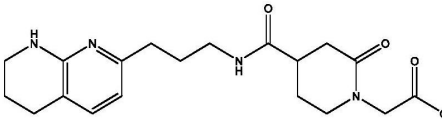
,

,

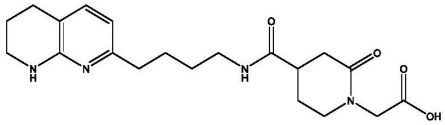
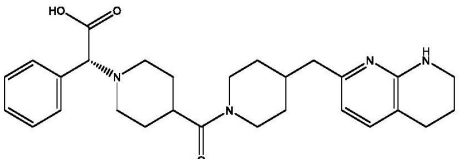
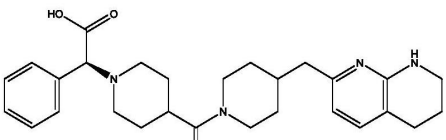
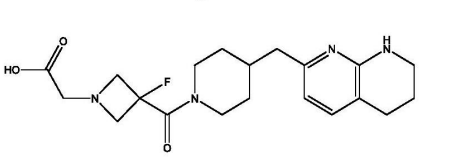
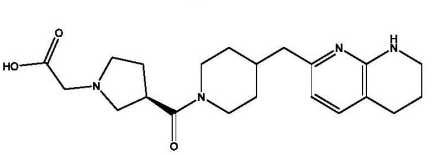

，

，

，

和

，或其药学上可接受的盐。

4.根据权利要求1所述的化合物，其中所述化合物选自由如下组成的组：


，

，

，，

，

，

，

，

，


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

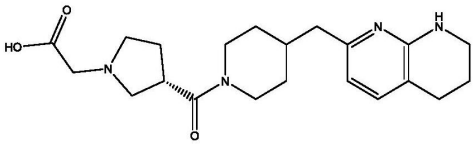
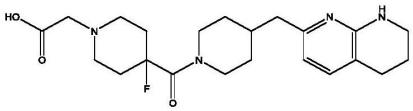
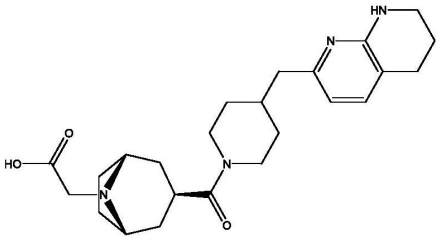
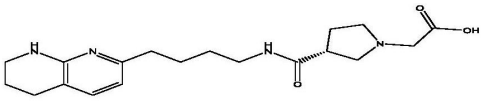
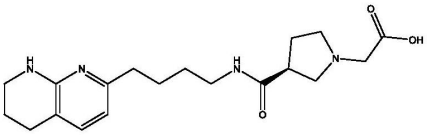
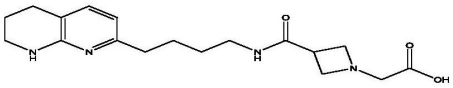
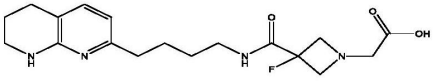
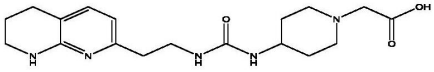
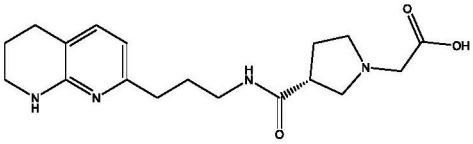
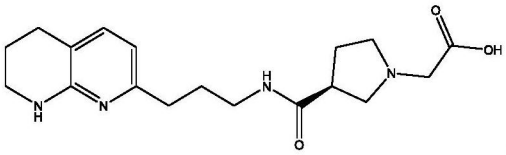
,

,

,

,

,

,

,

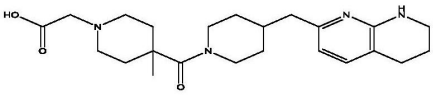
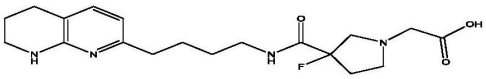
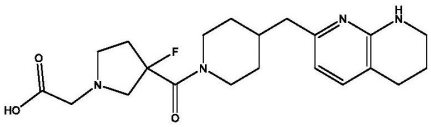
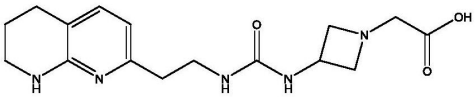
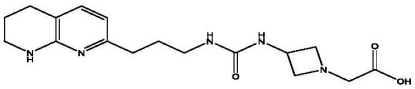
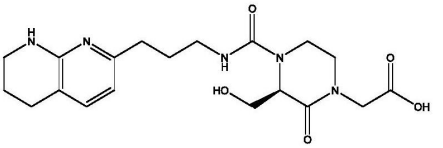
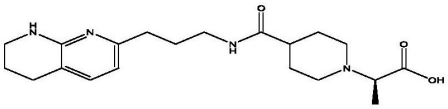
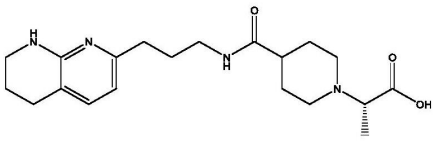
,

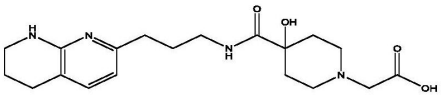
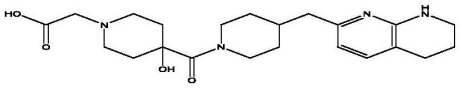
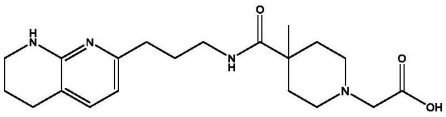
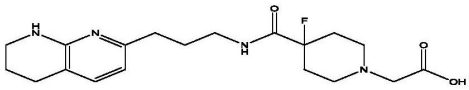
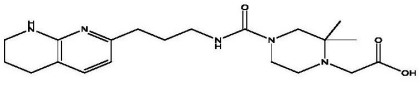
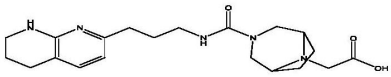
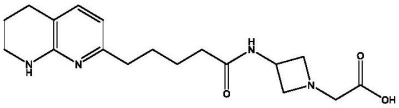
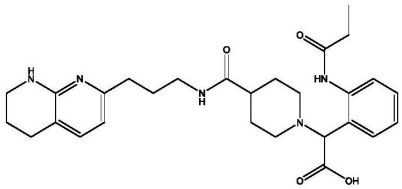
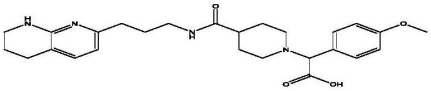
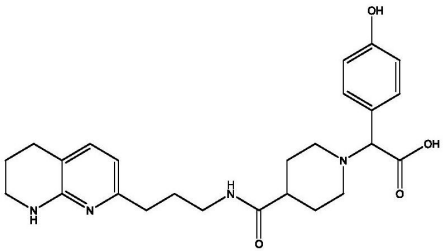
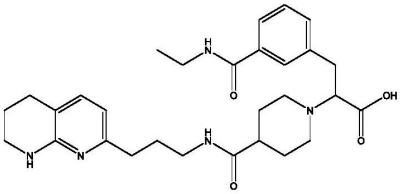
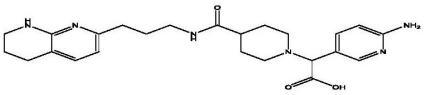
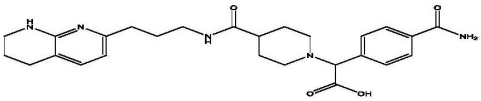
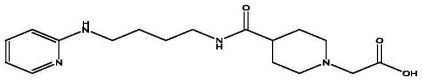
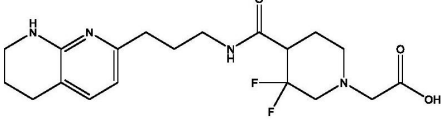
,

,

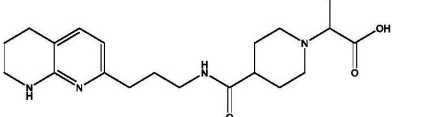
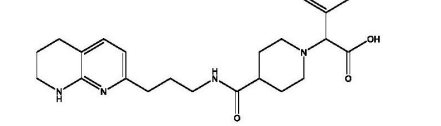

,

,

,

,

,

,

,

,

和

，或其药学上可接受的盐。

5.根据权利要求1所述的化合物，其中所述化合物选自由如下组成的组：


,

,

,

,

,

,

,

,

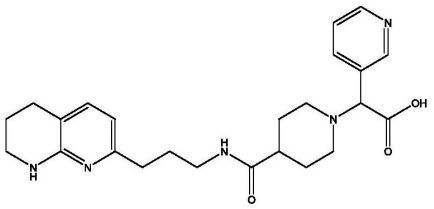
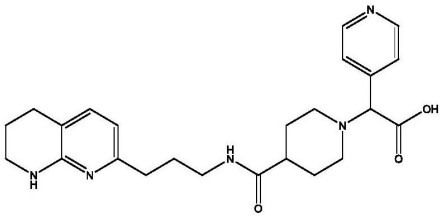
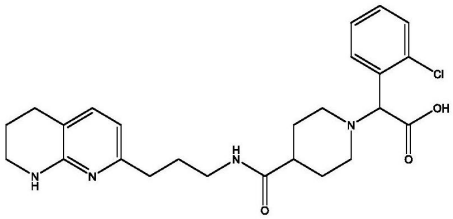
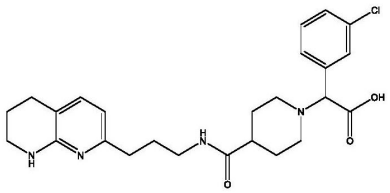
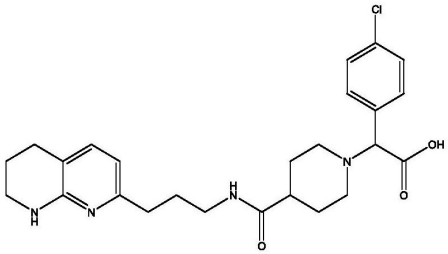
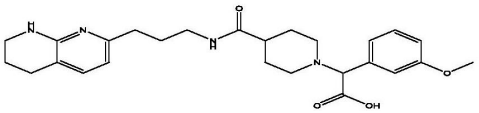
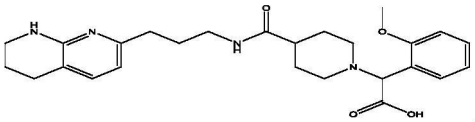

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

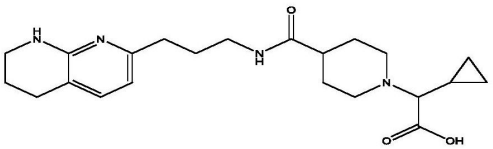
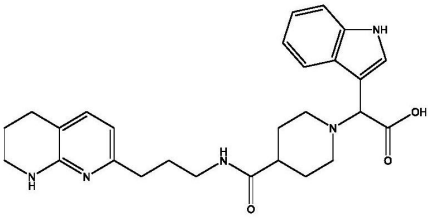
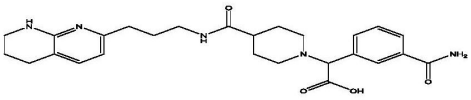
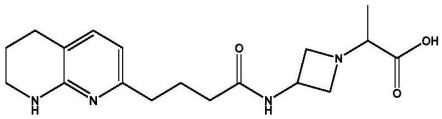
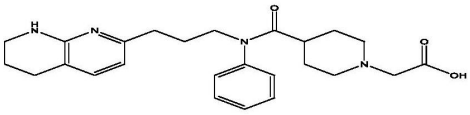
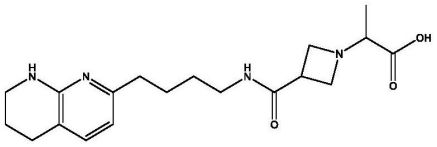
,

,

,

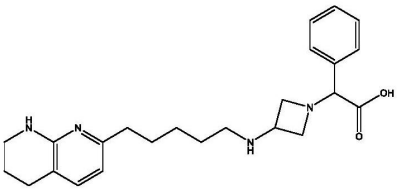
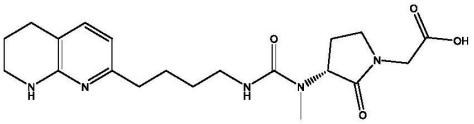
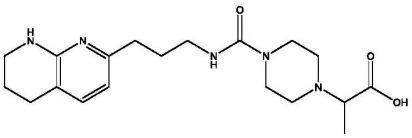
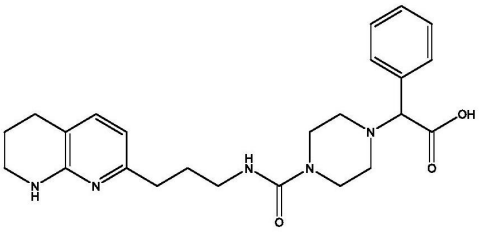
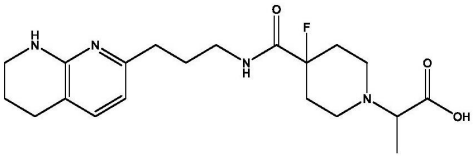
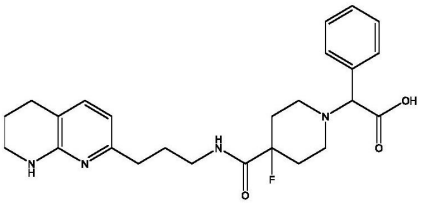
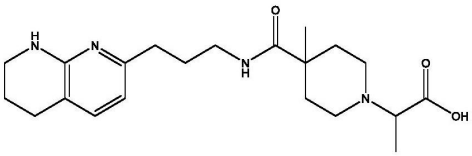
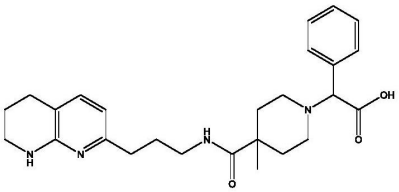
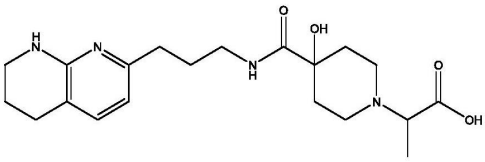
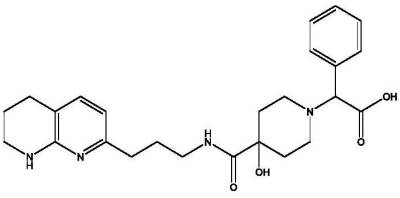
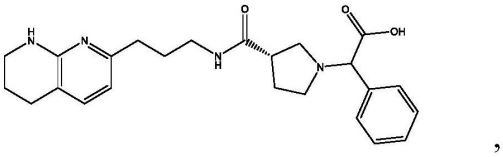
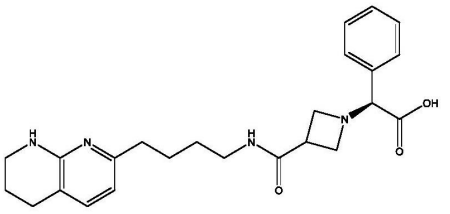
,

,

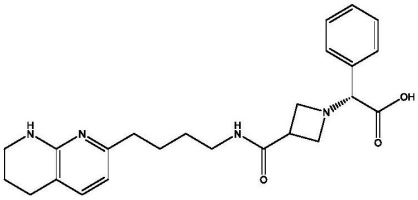
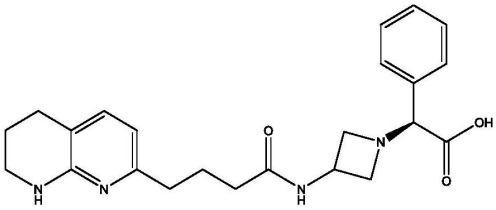

,

,

,

,

,

和

,或其药学上可接受的盐。

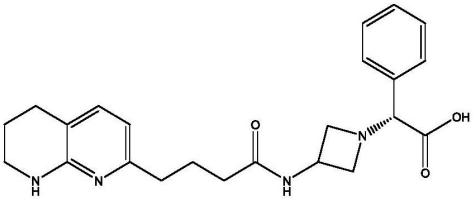
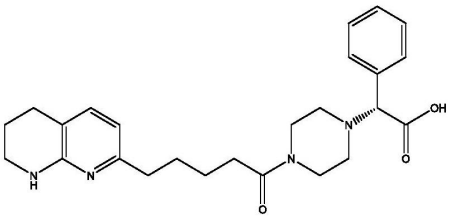
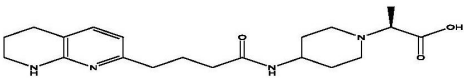
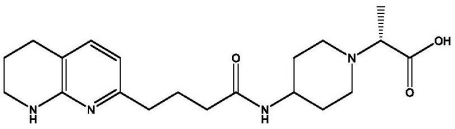
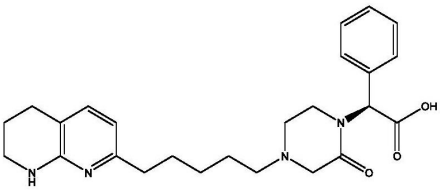
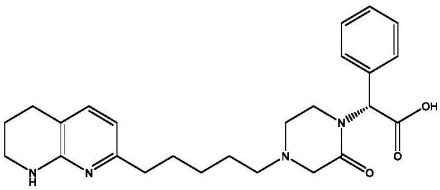
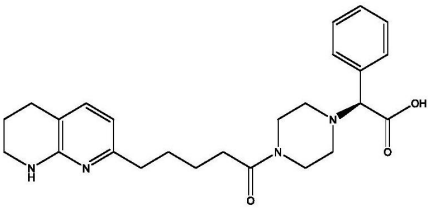
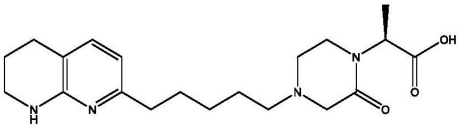
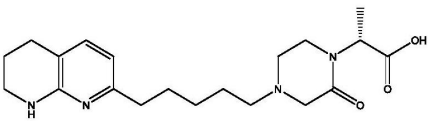
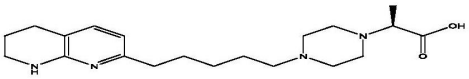
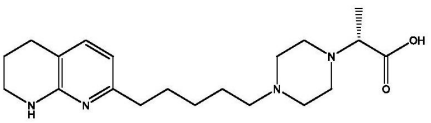
6.根据权利要求1所述的化合物,其中所述化合物选自由如下组成的组:

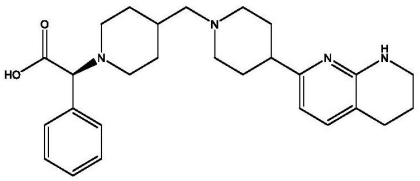

,

,

,

,

,

,

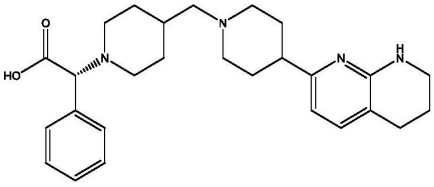
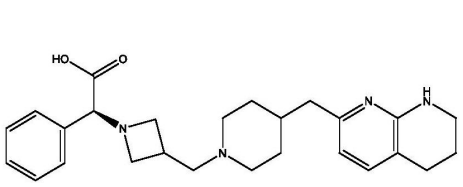

,

,

,

,

,

,

,

,

,

,

,

,

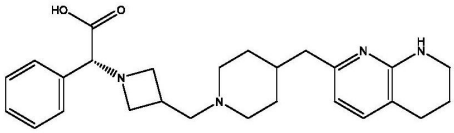
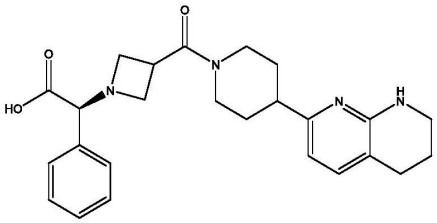
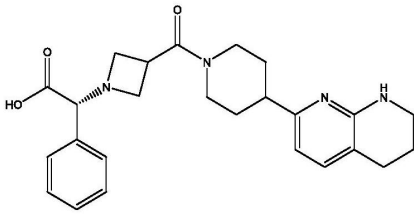
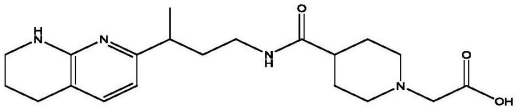
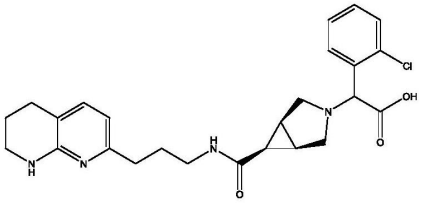
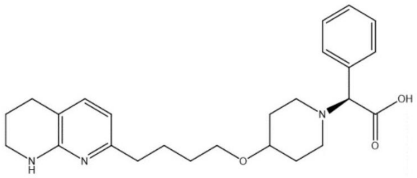
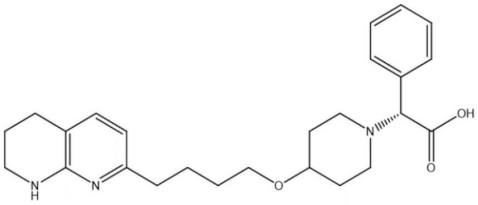
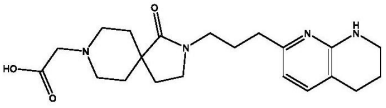
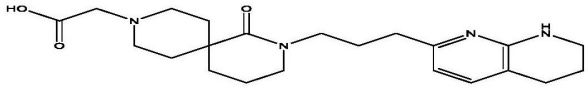
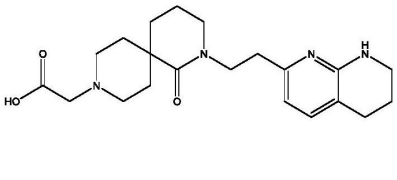
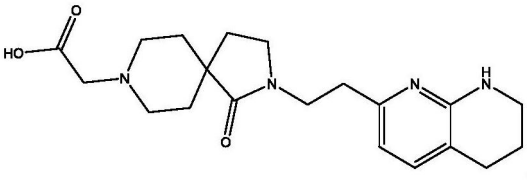
,

,

,

,

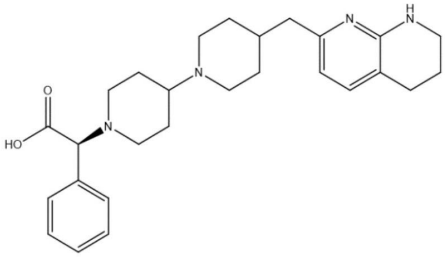
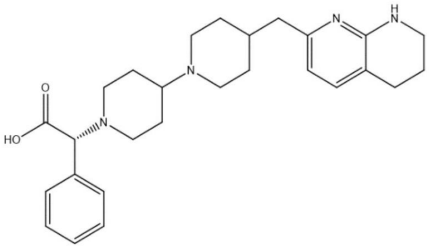
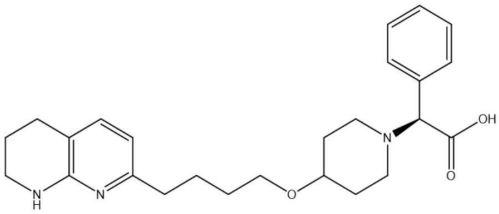
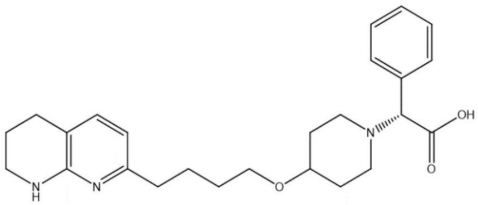
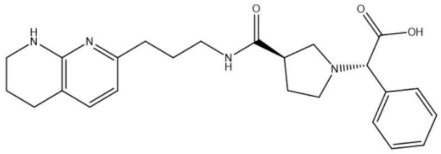
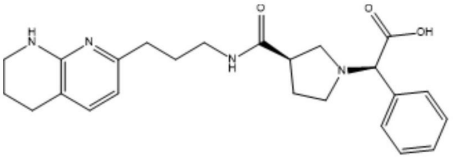
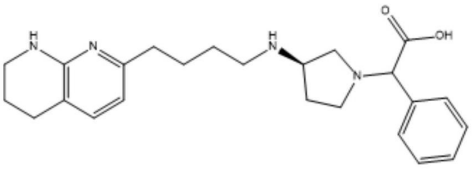
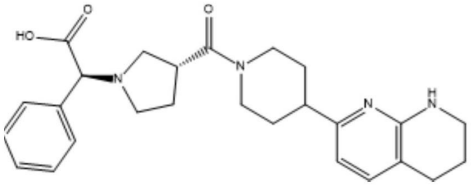
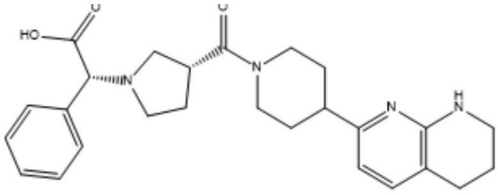

,

,

,

,

,

,

,

,

,

,

,

,

,

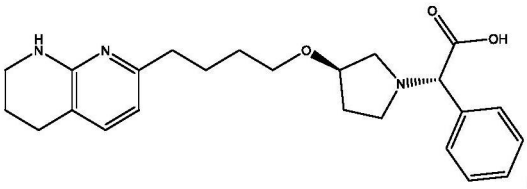
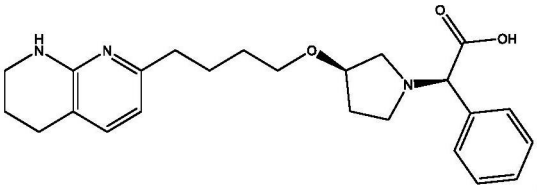
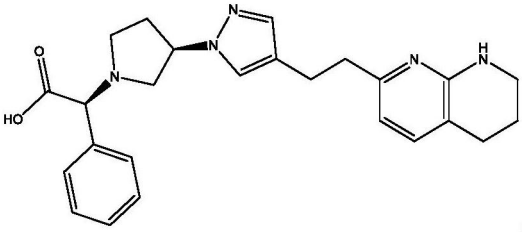
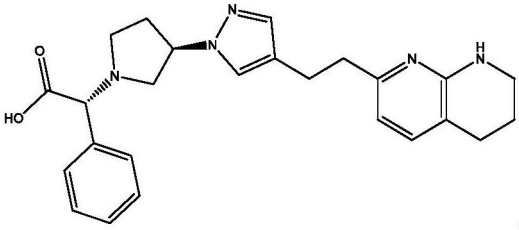
,

,

,

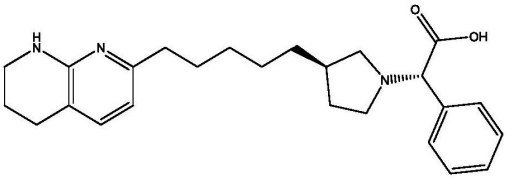
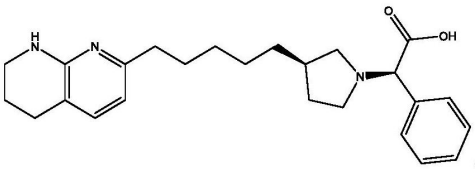
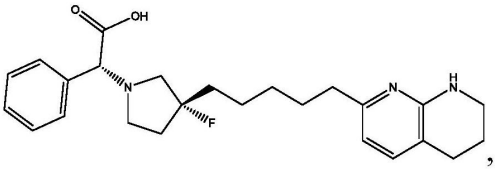
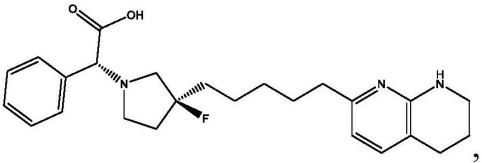
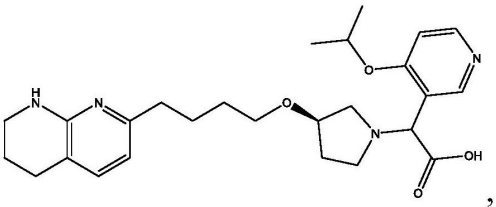
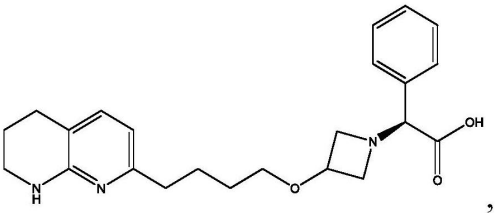
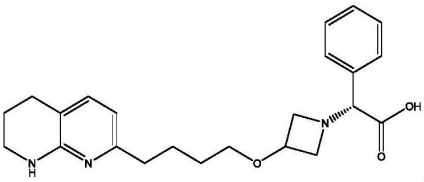
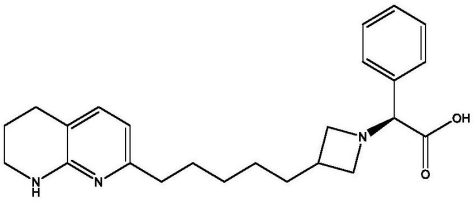
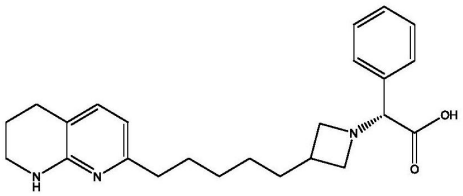
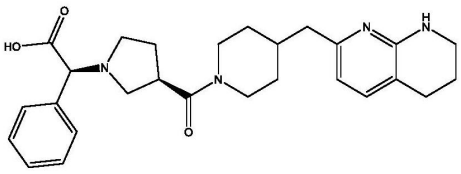
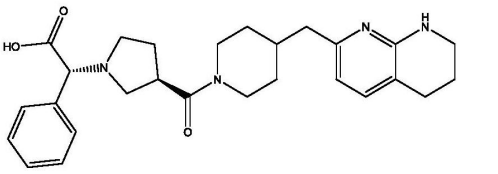
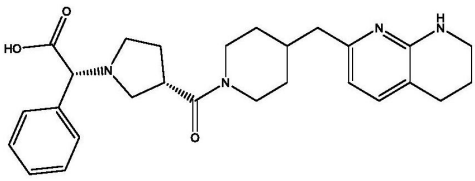
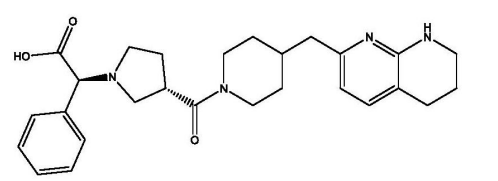

,

,

,

,

,

,

,

,

,

和

或其药学上可接受的盐。

7.根据权利要求1所述的化合物，其中所述化合物选自由如下组成的组：

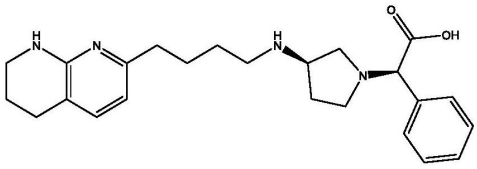
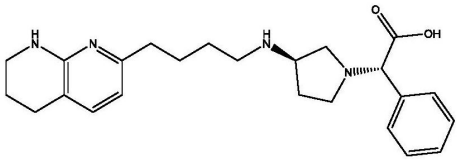
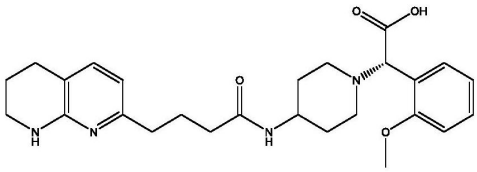
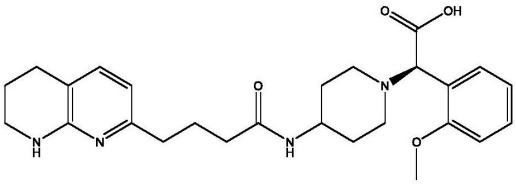
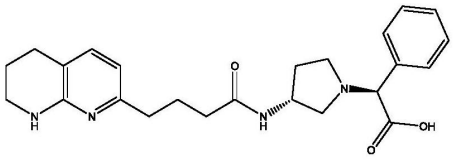
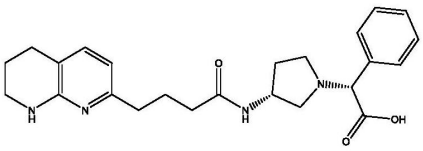
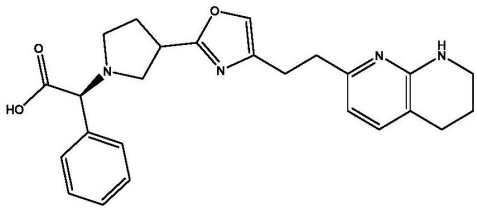
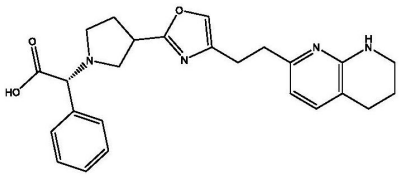
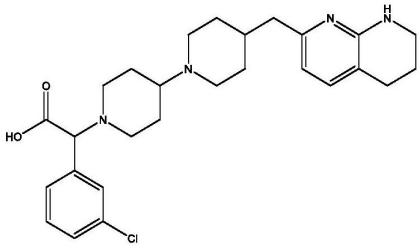
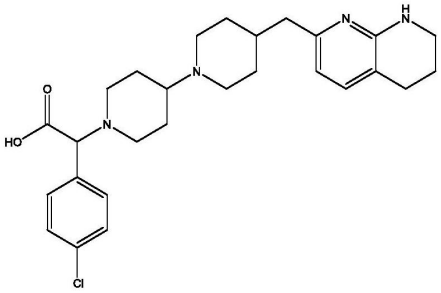
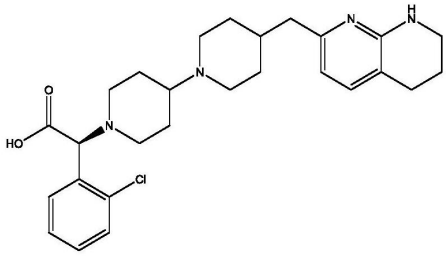

,

,

,

,

,

,

,

和

,
或其药学上可接受的盐。

8.根据权利要求1所述的化合物，其中所述化合物选自由如下组成的组：1.

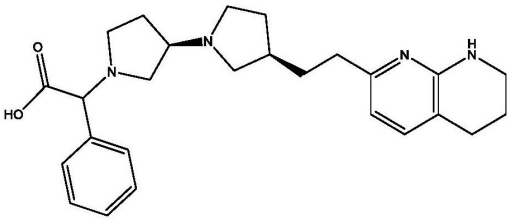
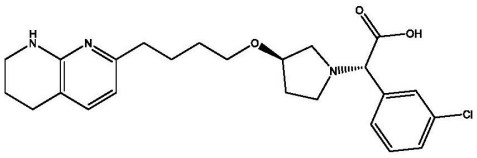
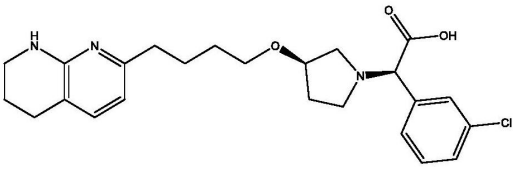
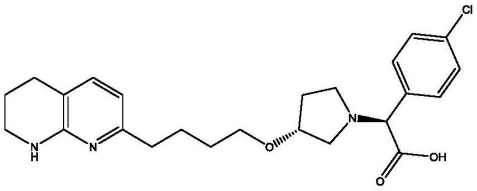
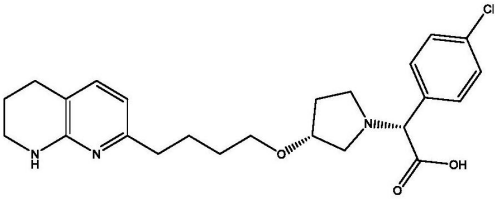
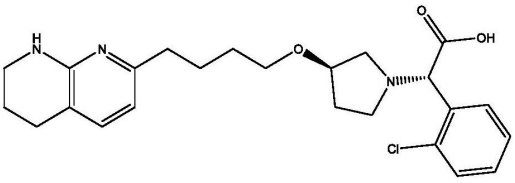
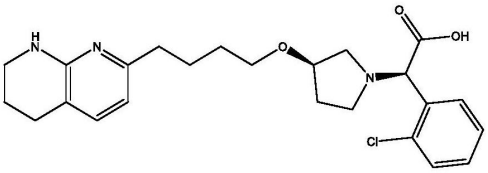
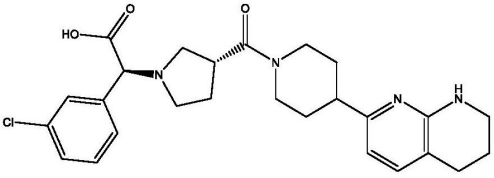
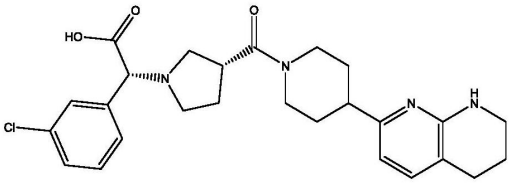
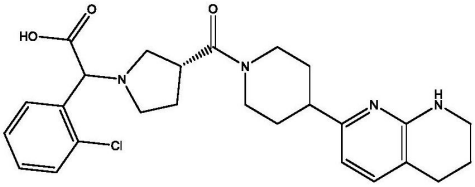
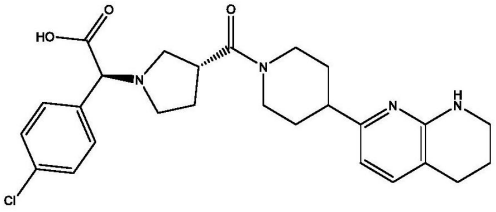
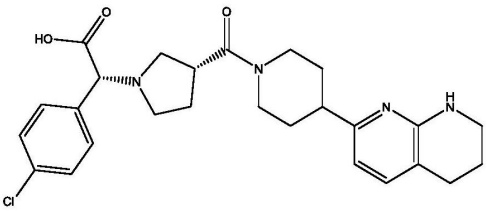

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

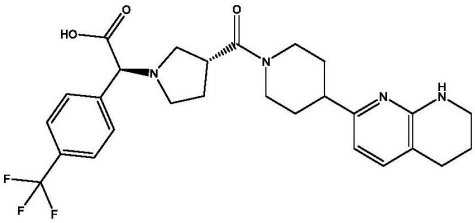
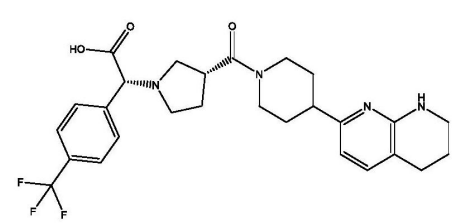
,

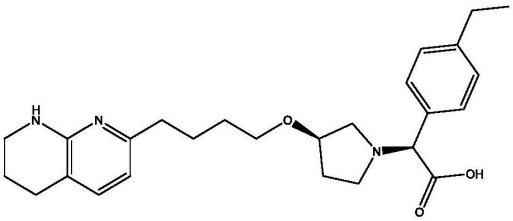
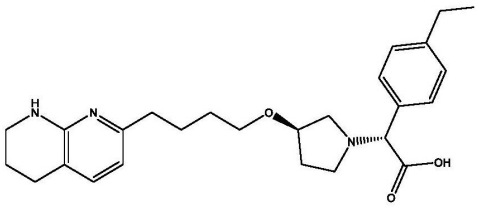
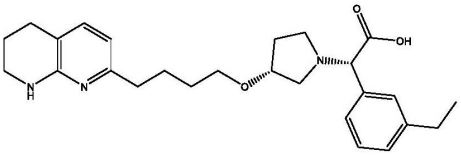
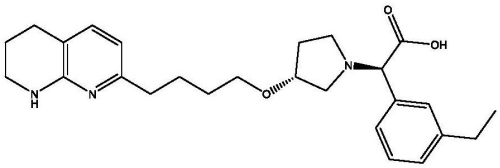
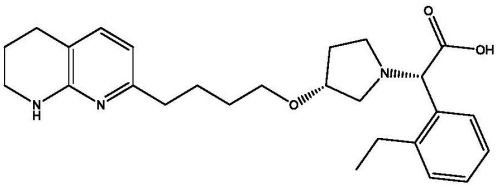
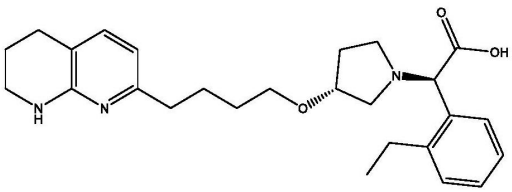
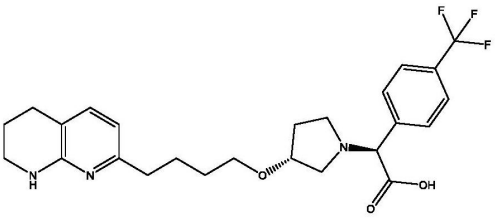
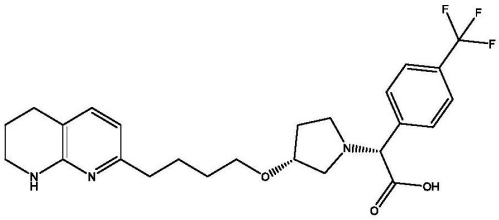
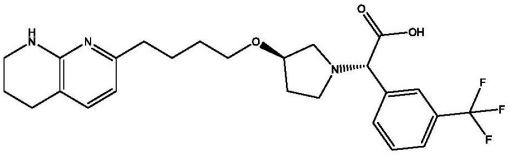
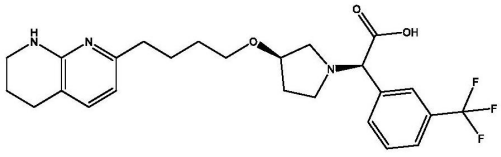
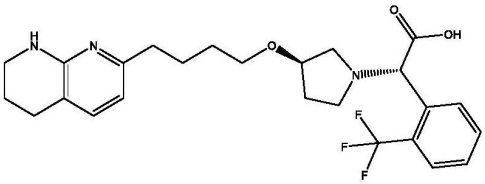
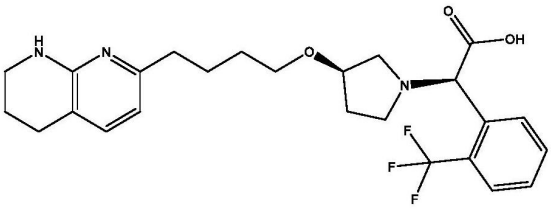

,

,

,

,

,

,

,

,

,

,

,

,

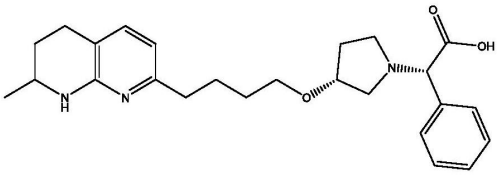
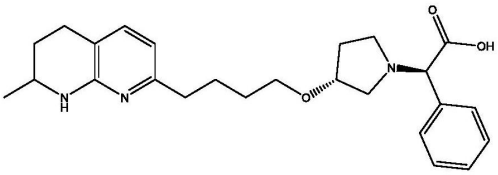
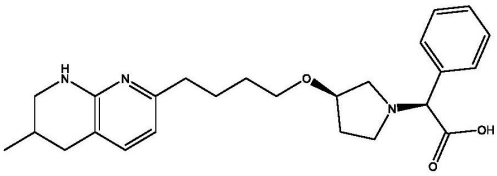
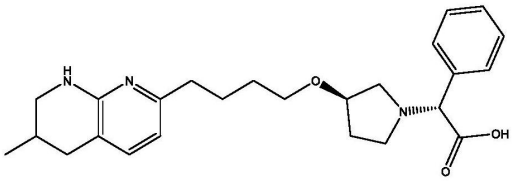
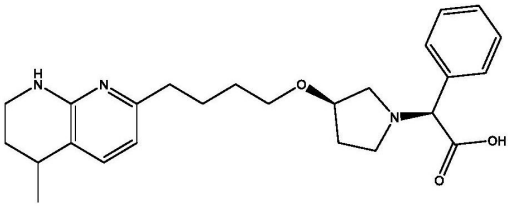
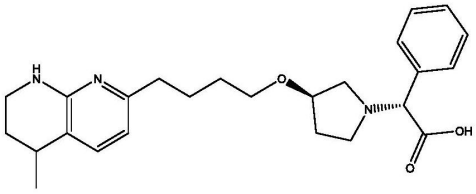
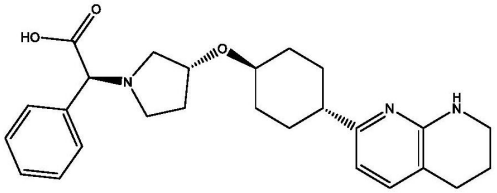
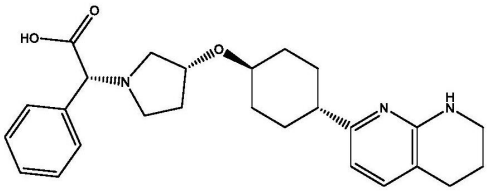
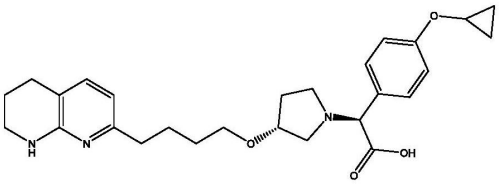
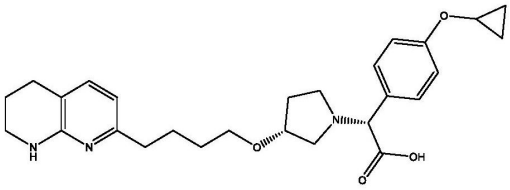
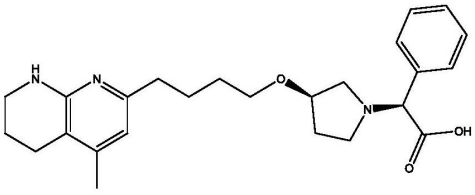
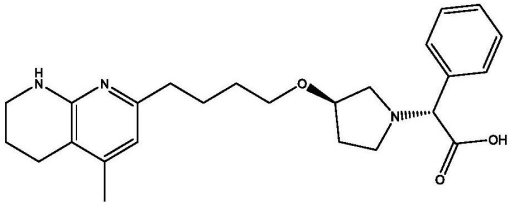

,

,

,

,

,

,

,

,

,

,

,

,

,

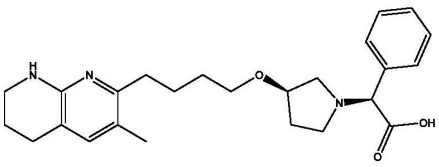
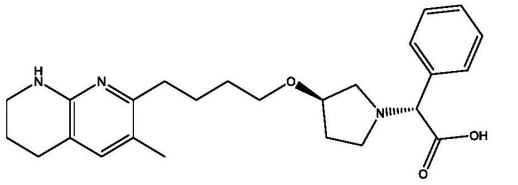
,

,

,

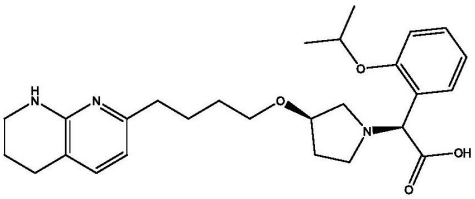
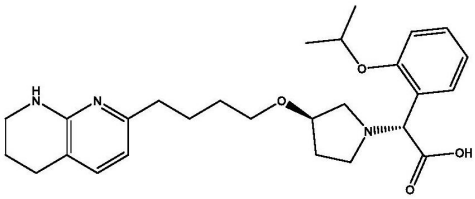
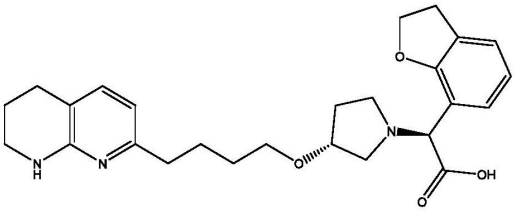
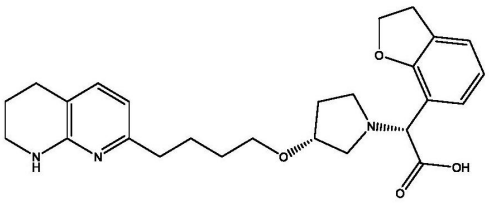
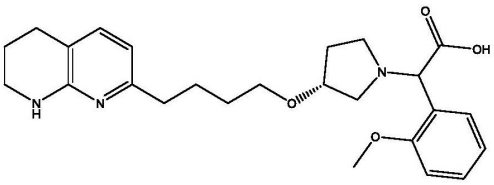
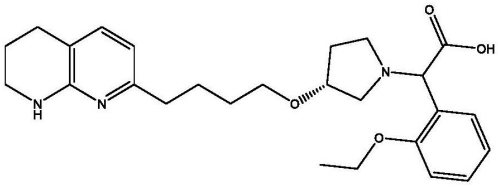
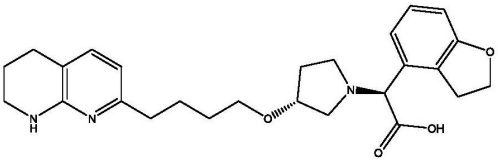
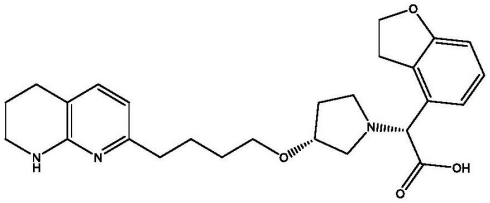
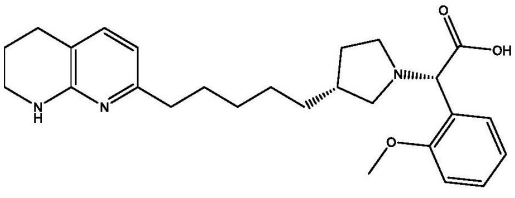
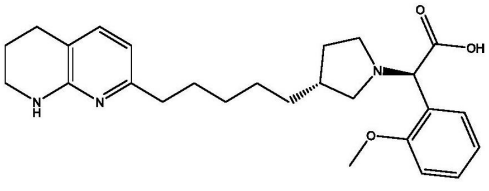
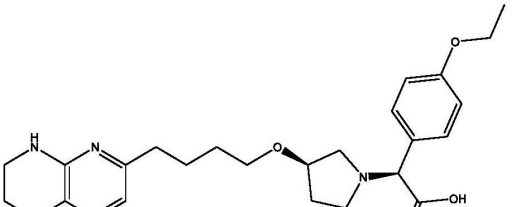
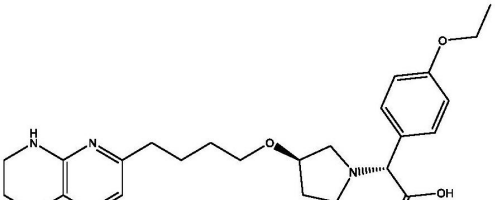

,

,

,

,

,

,

,

,

,

,

和

,或其药学上可接受的盐。

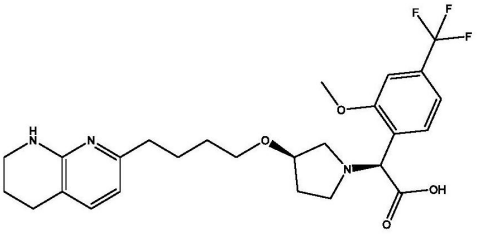
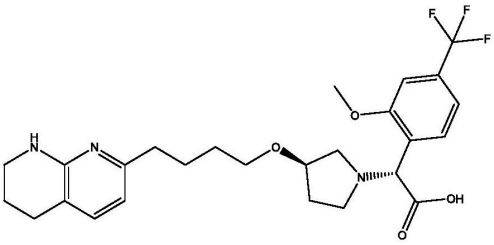
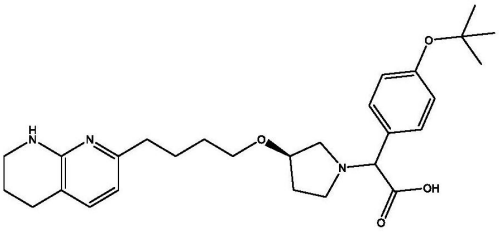
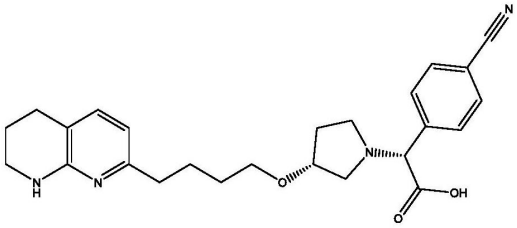
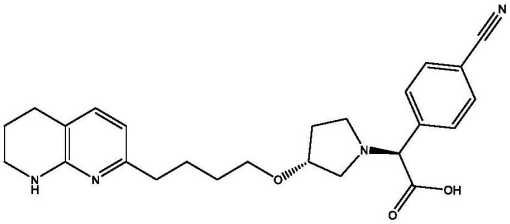
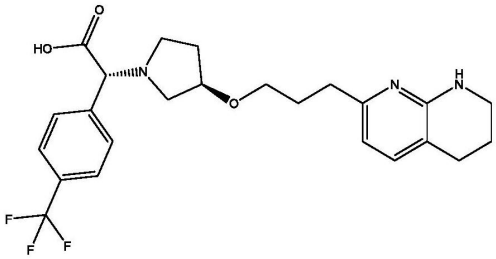
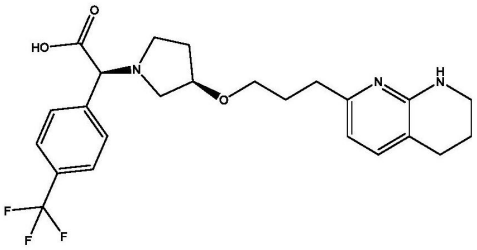
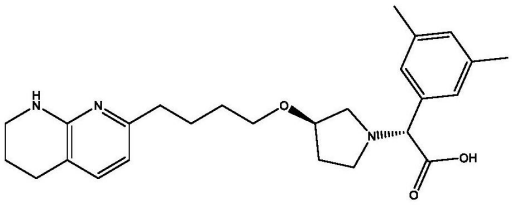
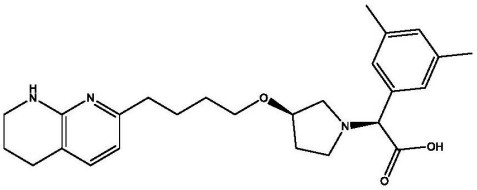
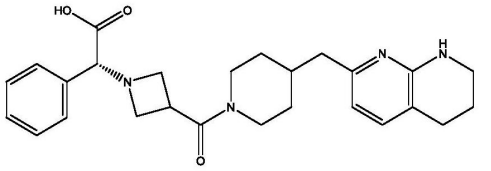
9.根据权利要求1所述的化合物,其中所述化合物选自由如下组成的组:


,

,

,

,

,

,

,

,

,

,

,

,

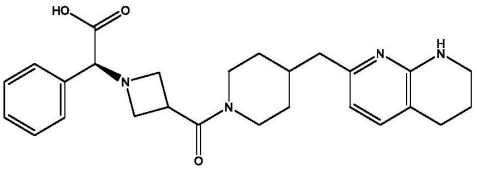
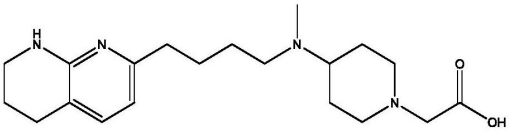
,

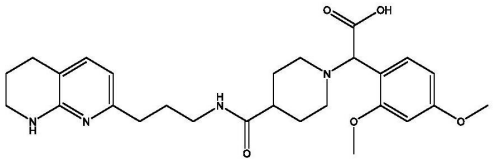
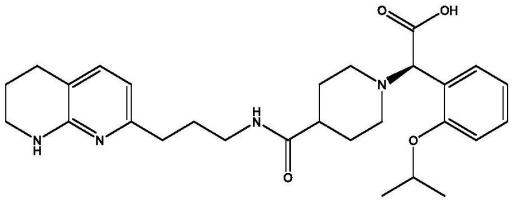
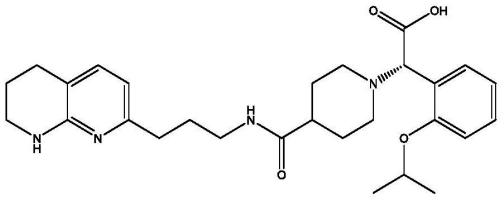
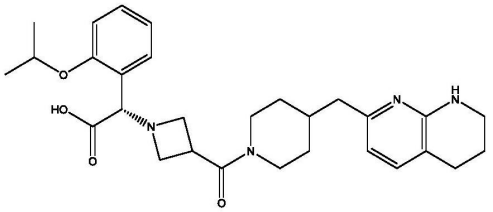
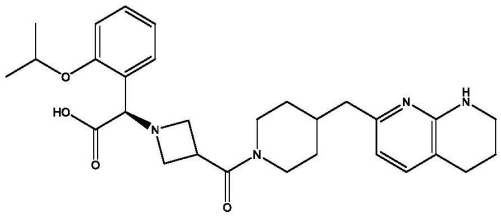
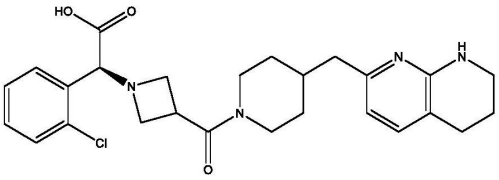
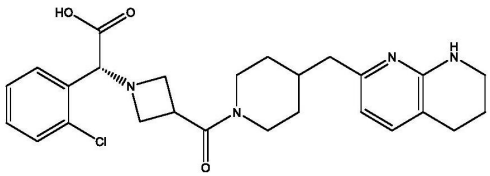
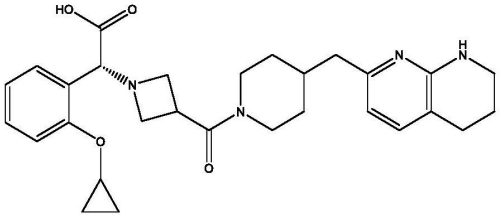
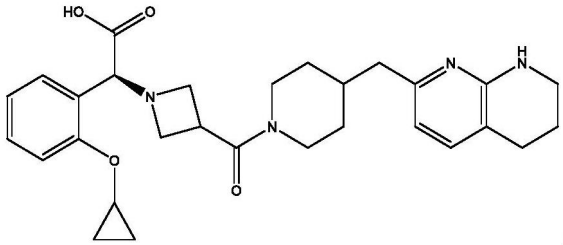
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

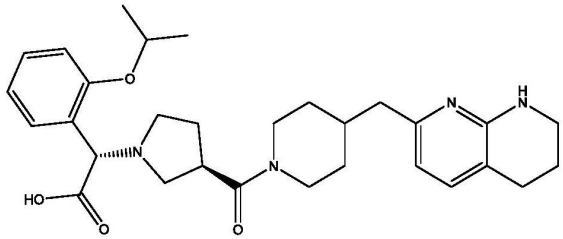
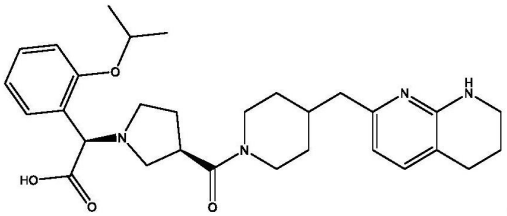

,

,

,

,

,

,

,

,

,

,

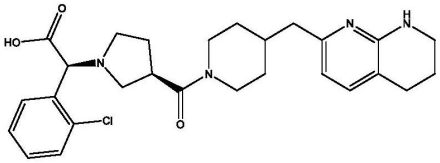
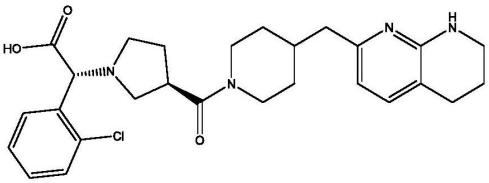
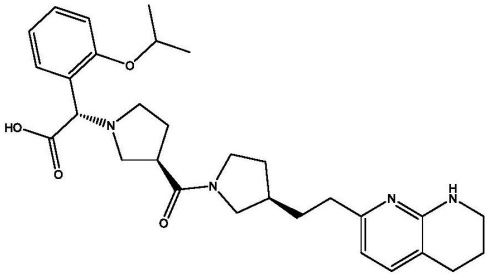
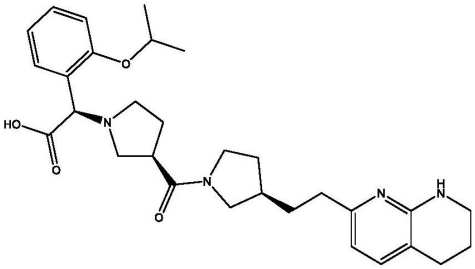
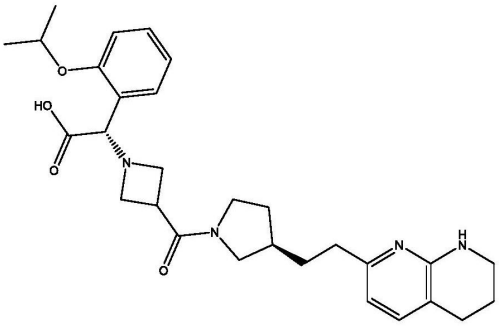
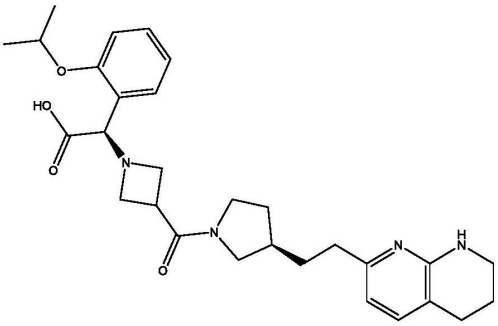
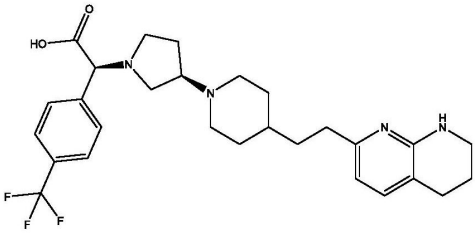
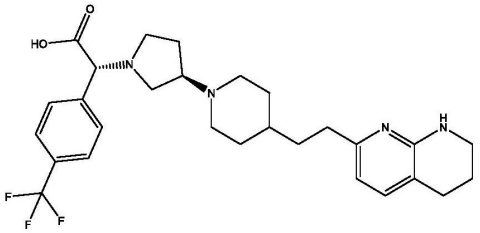
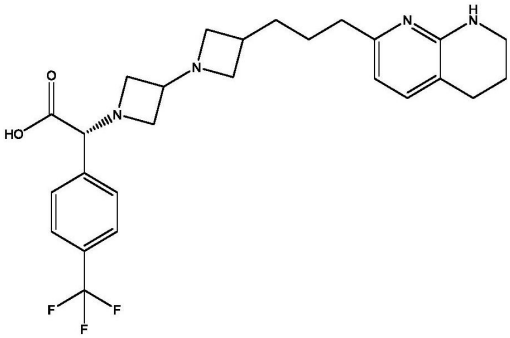
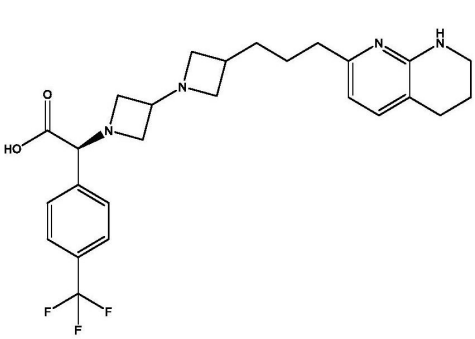
,

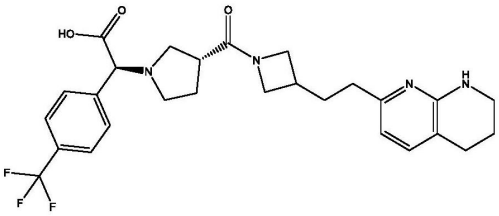
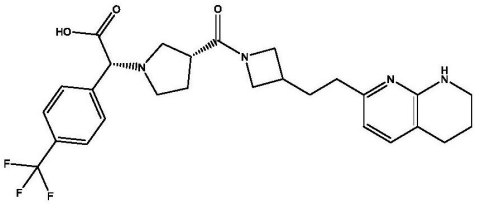
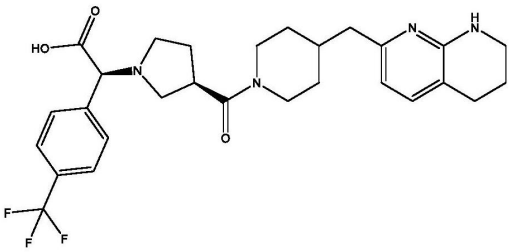
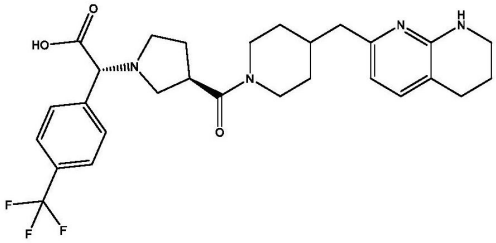
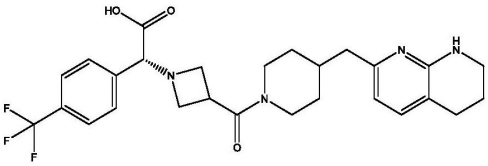
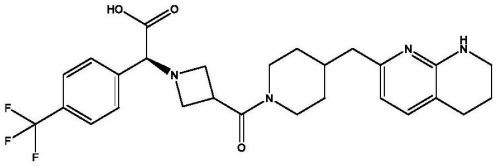
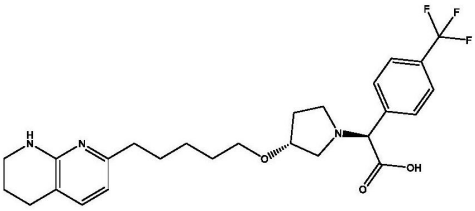
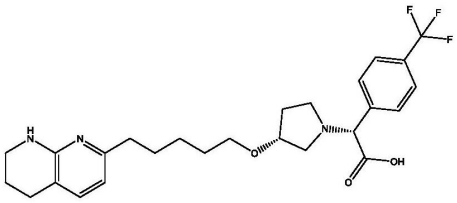
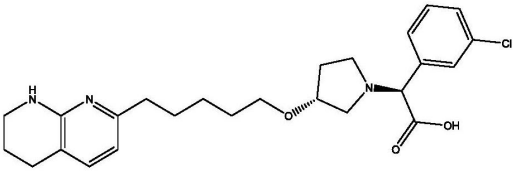
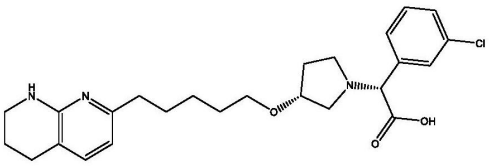
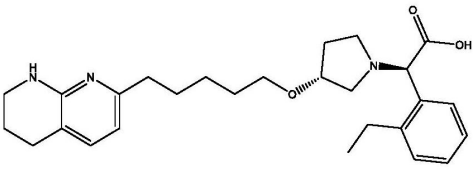
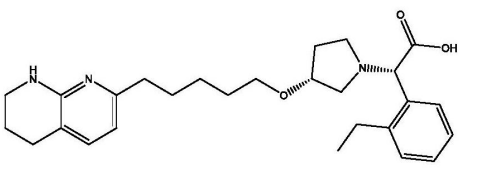
,

,

,


,

,

,

,

,

,

,

和

,
或其药学上可接受的盐。

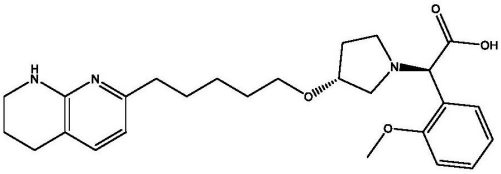
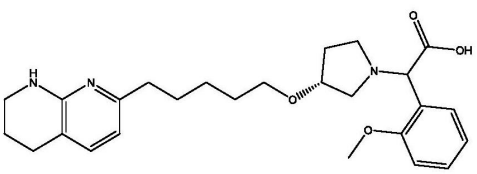
10.根据权利要求1所述的化合物,其中所述化合物选自由如下组成的组:

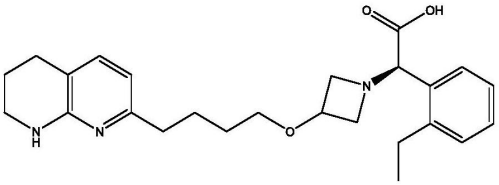
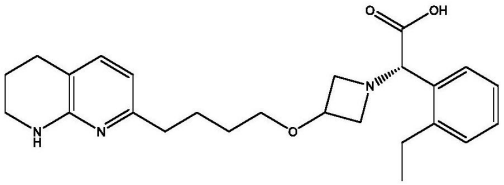
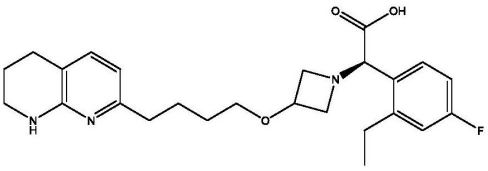
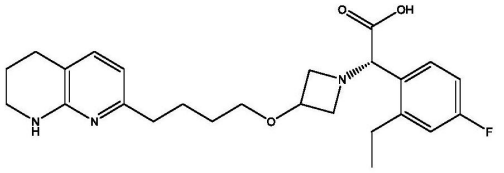
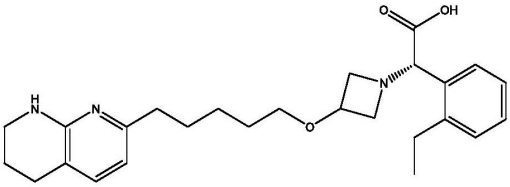
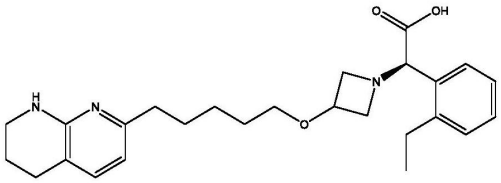
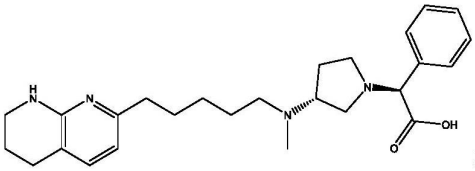
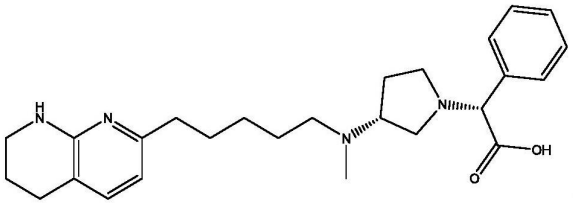

,

,


,

,

,

,

,
,

,

,

,

,

,

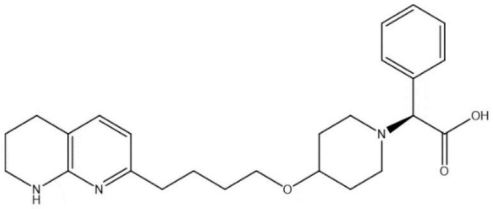
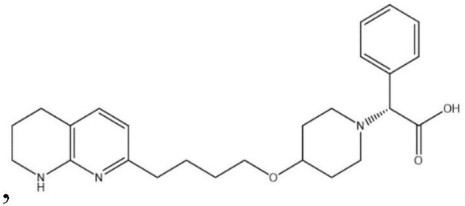
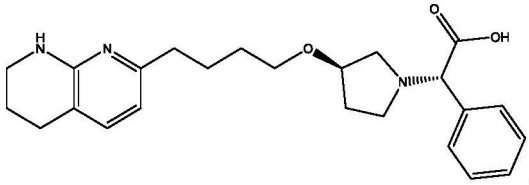
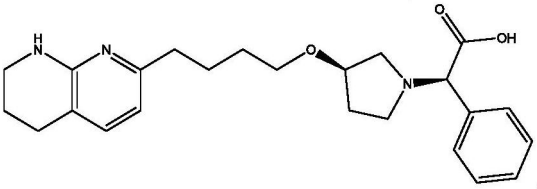

,

,

,

,

,

,

,

,

,

,

,

,

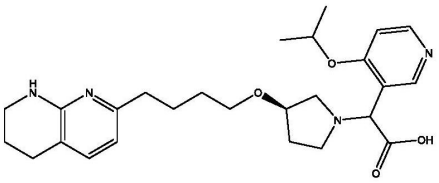
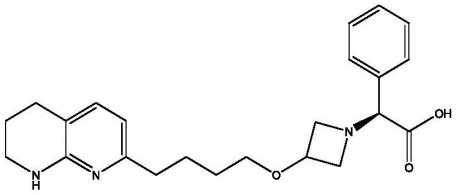
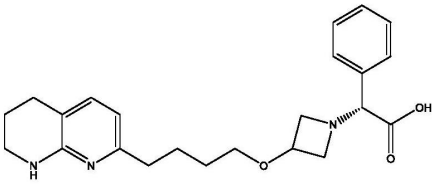
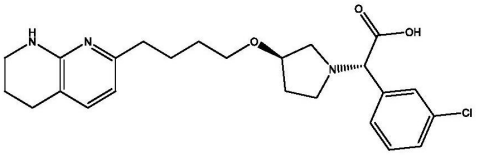
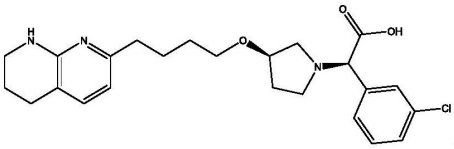
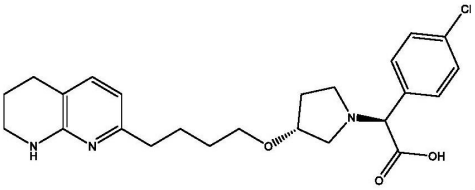
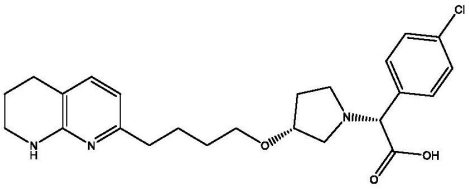
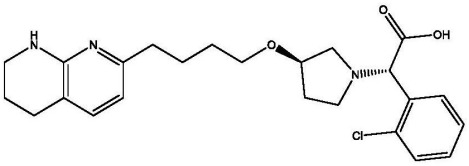
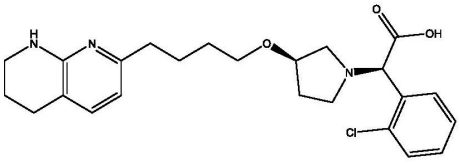
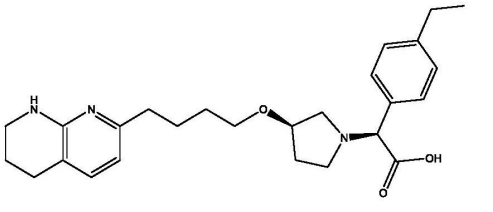
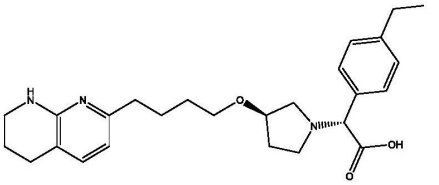
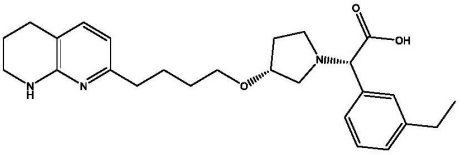
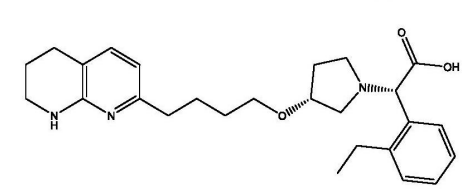
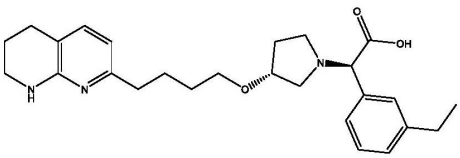
,

,

,

,


,

,

,

,

,

,

和

,或其药学上可接受的盐。

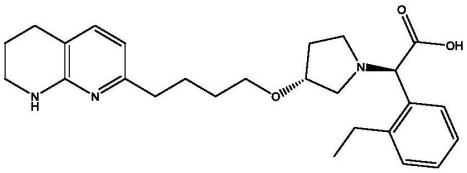
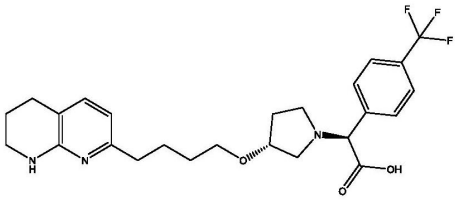
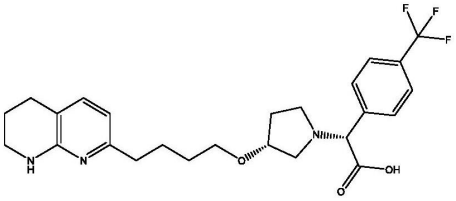
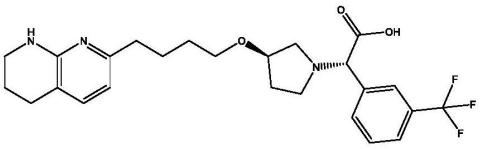
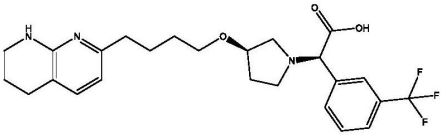
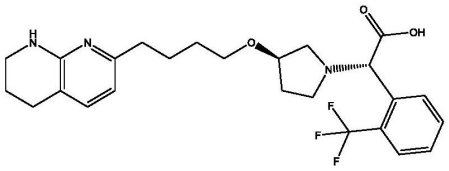
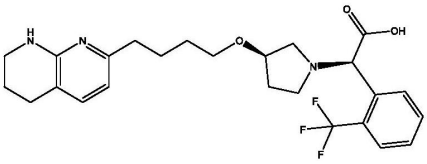
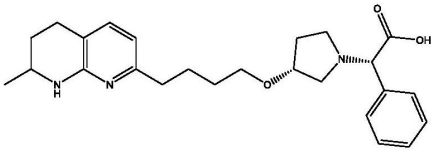
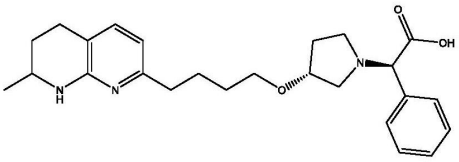
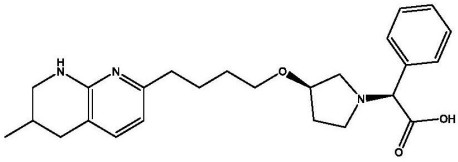
11.根据权利要求1所述的化合物,其中所述化合物选自由如下组成的组:


,

,

,

,

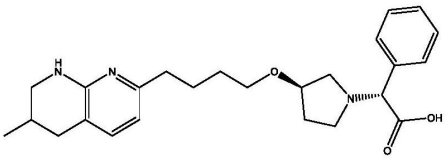
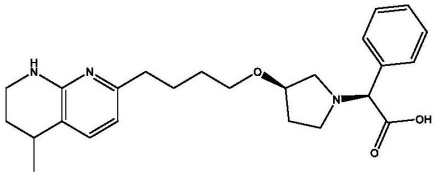

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

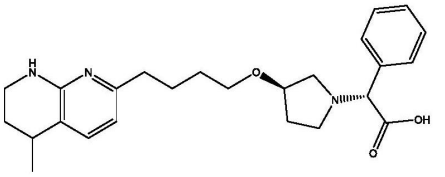
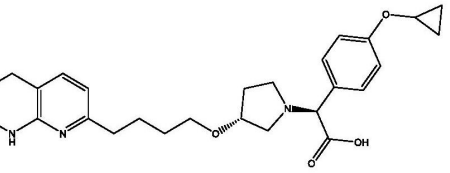
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

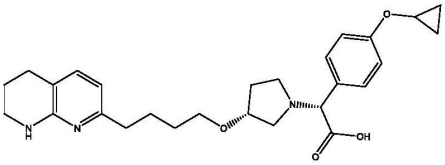
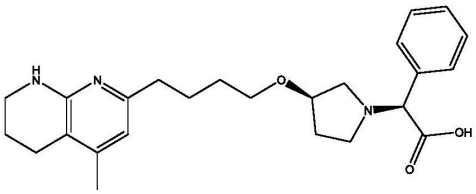
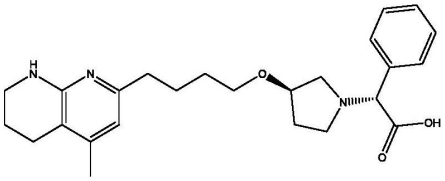
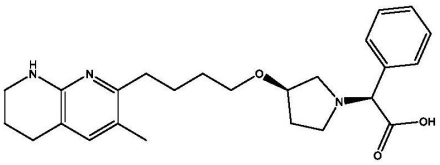
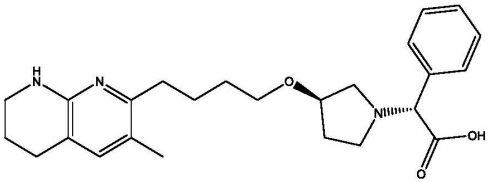
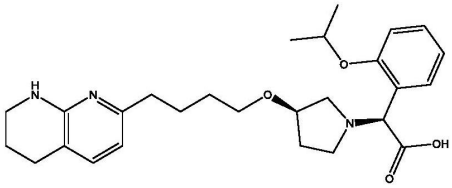
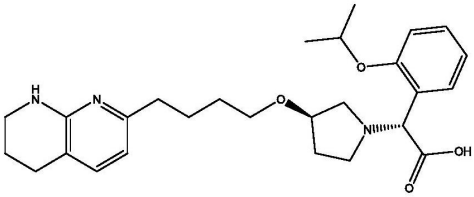
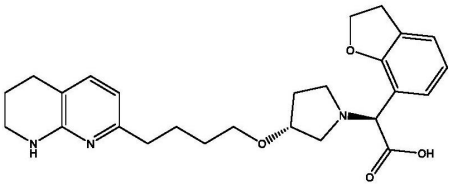
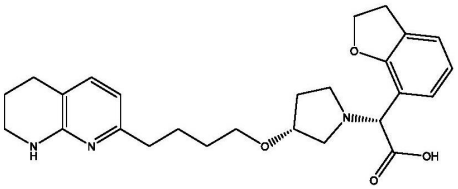
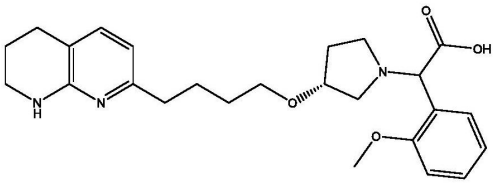
,

,

,

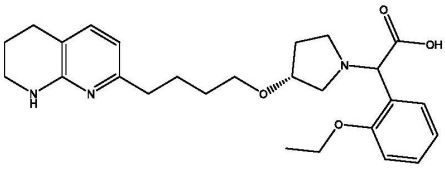
,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

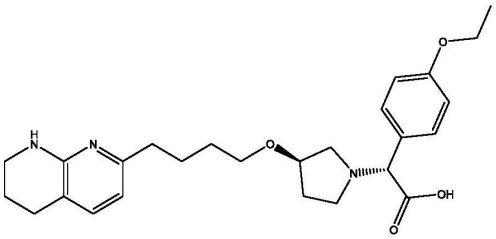
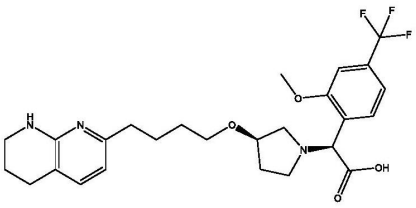
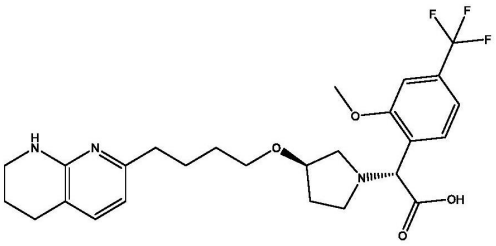
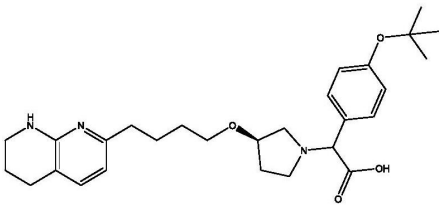
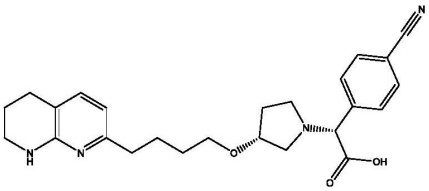
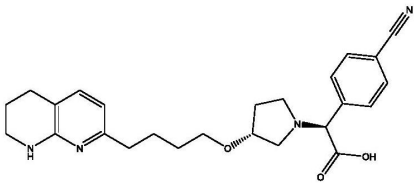
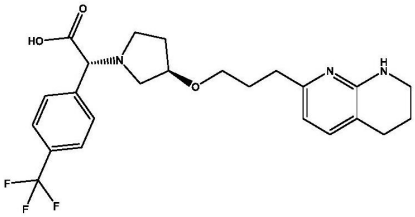
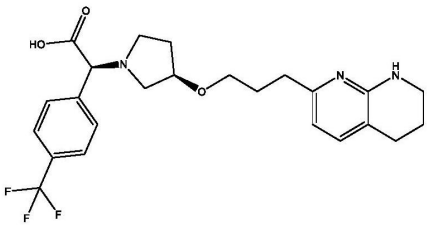
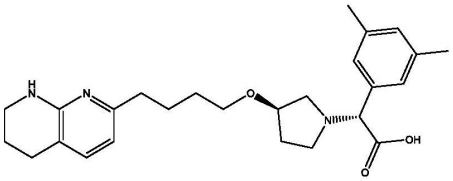
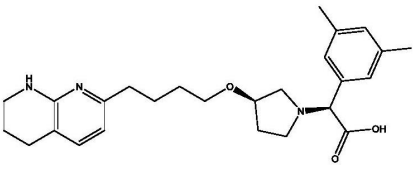
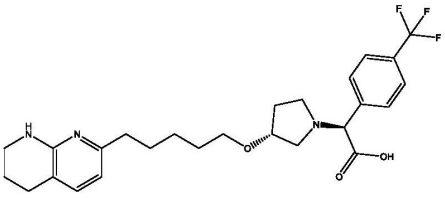
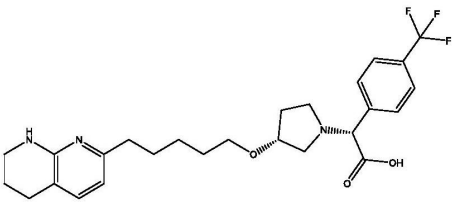
,

,

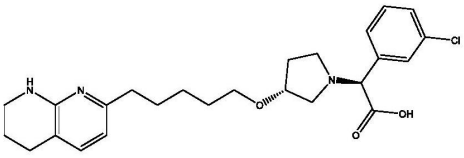
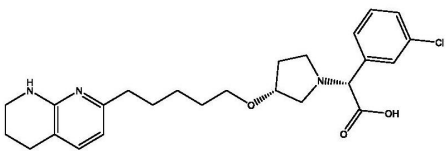
,

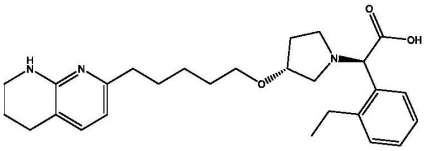
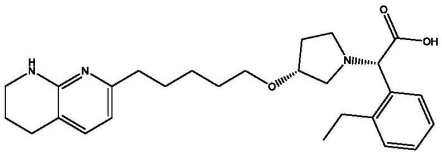
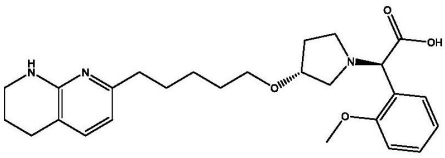
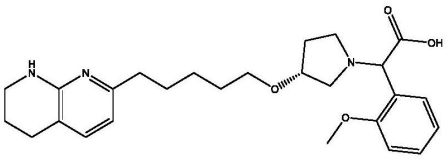
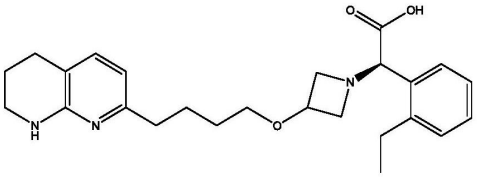
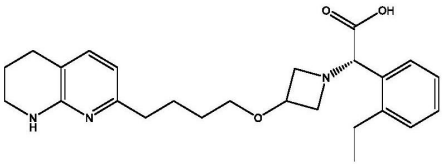
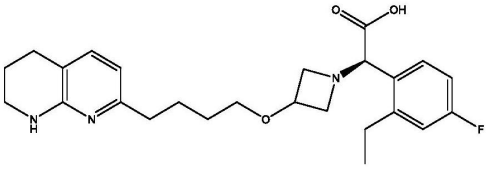
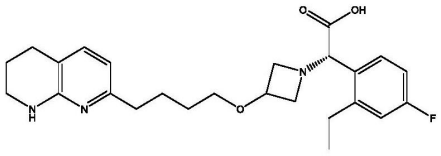
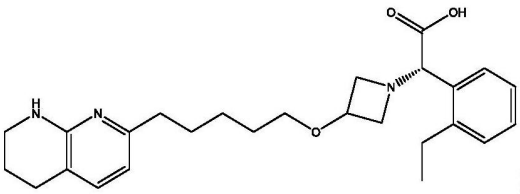
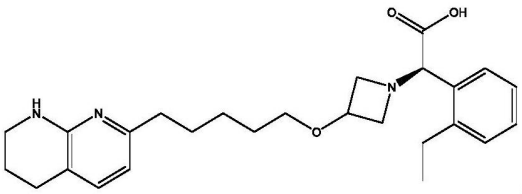
,

,

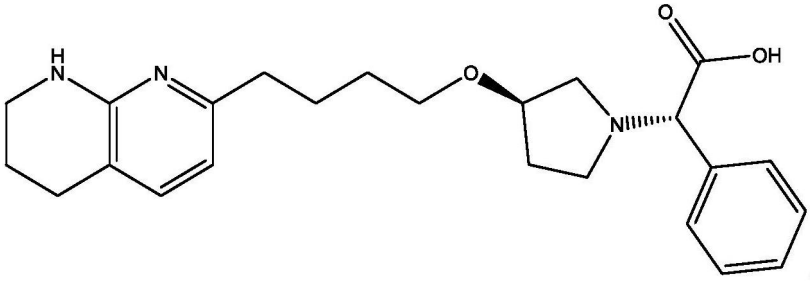

,

,

,

,

,

,

,

,

,

,

,

,

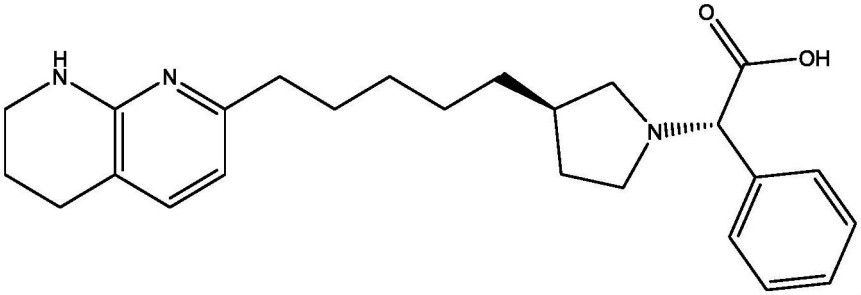
,

,

,

,

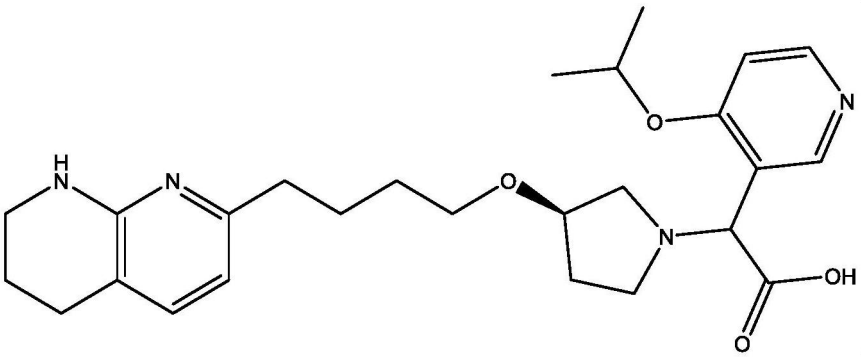

,

,

,

,

,

,

,

,

和

，或其药学上可接受的盐。

12.根据权利要求1所述的化合物，其中所述化合物选自由如下组成的组：

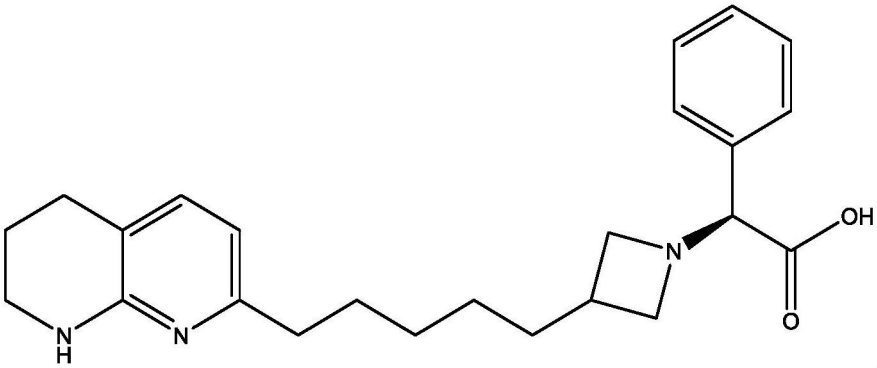

，


H
N
N
O
OH
N

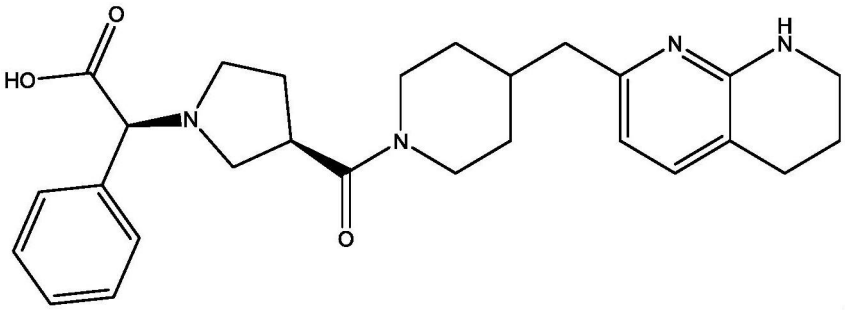
,


O
N
H
N
N
O
N
OH
O

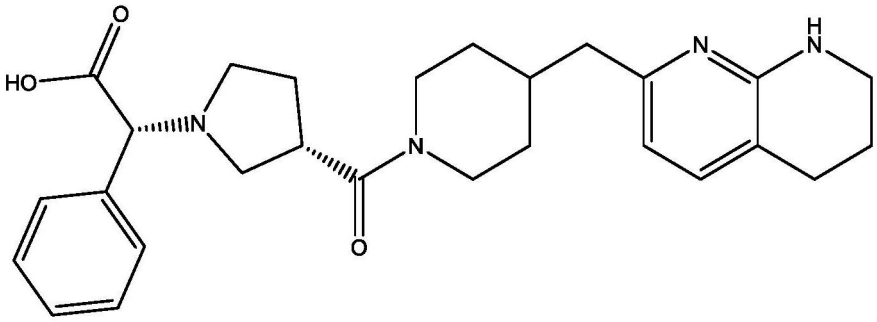
,


OH
N
O
N
H
N

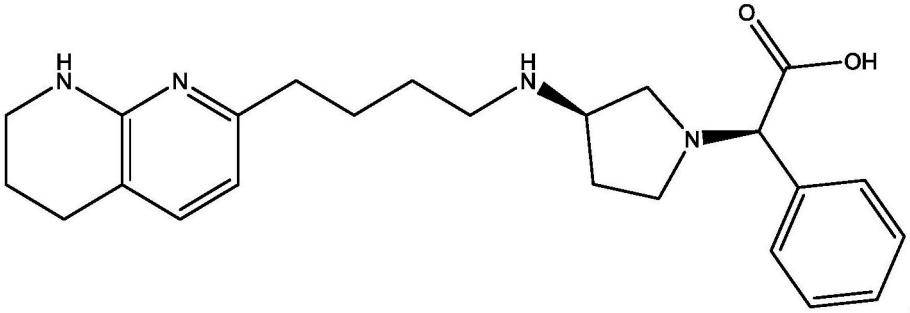
,

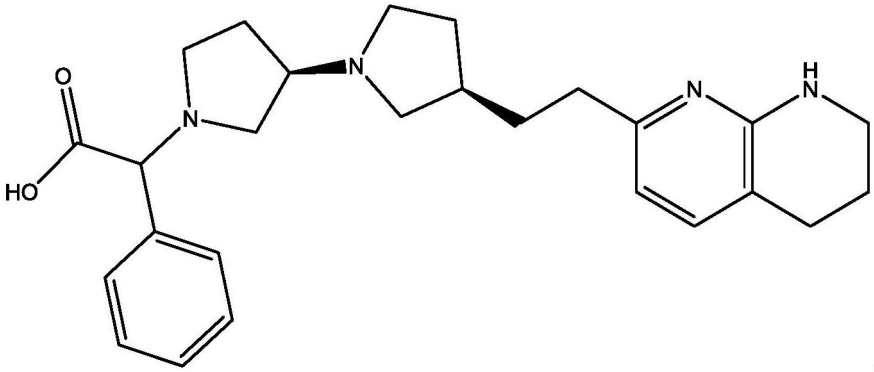

O
HO
N
N
O
N
H
N

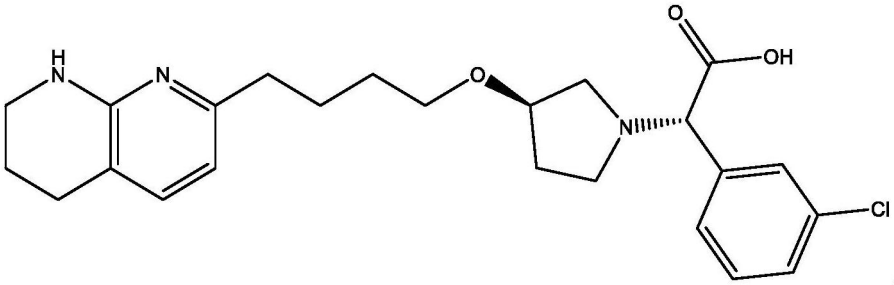
,

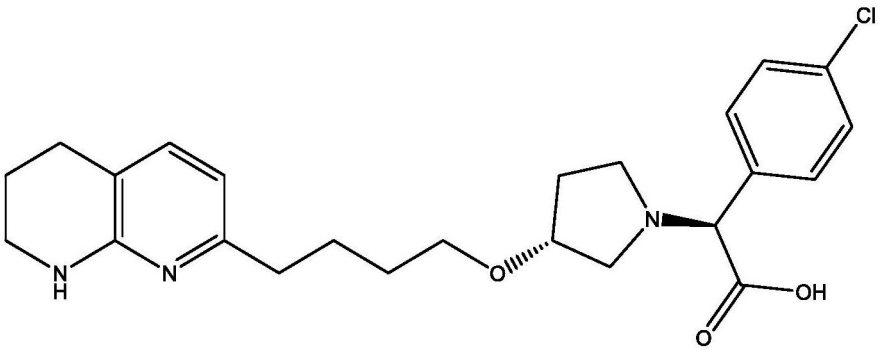

O
HO
N
N
O
N
H
N

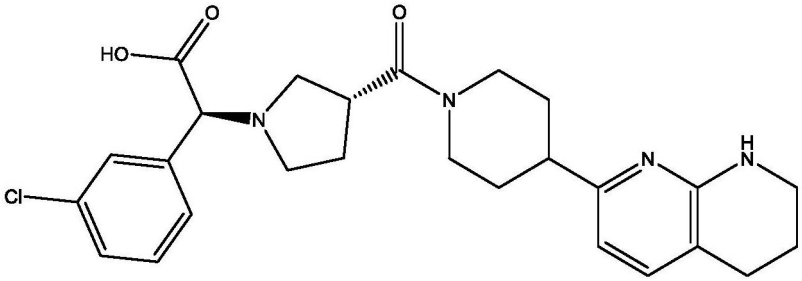
,

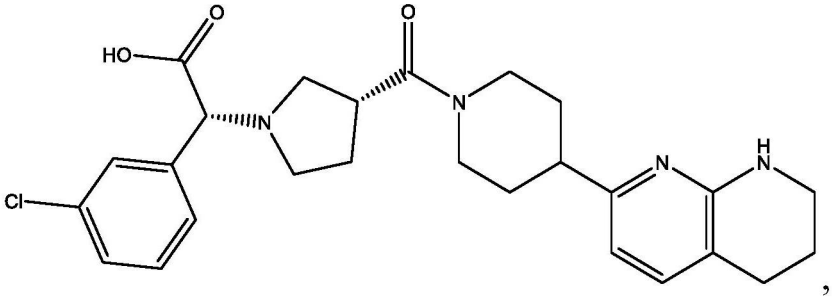

,


,

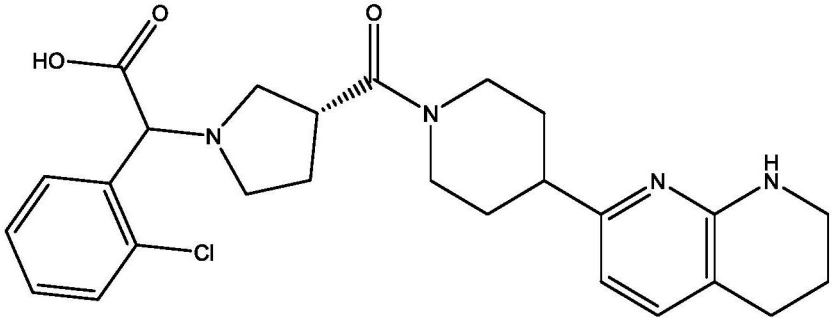

,


,

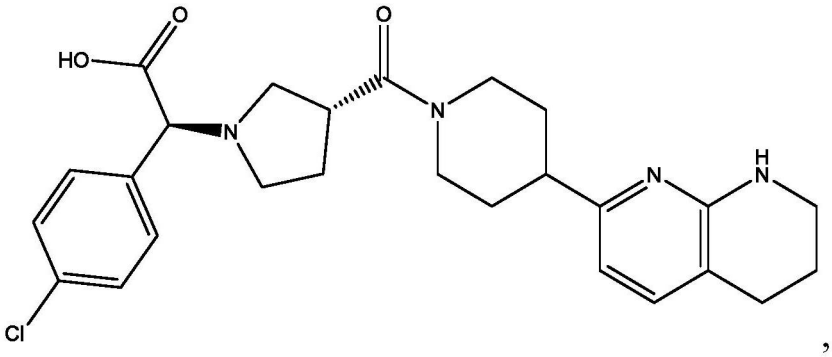

,


O
HO
O
N
N
N
H
N
Cl

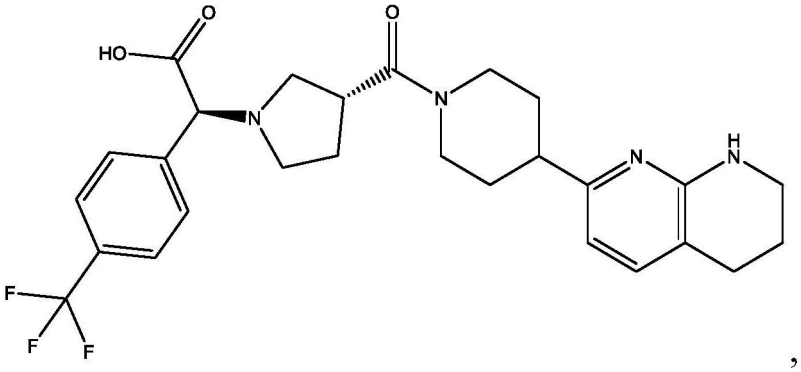
,


O
HO
O
N
N
N
H
N
Cl

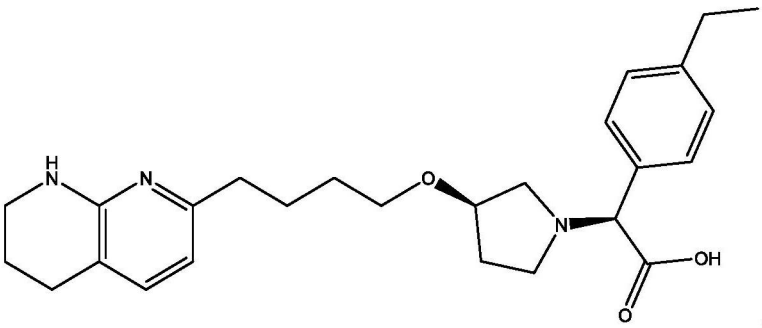
,


O
HO
O
N
N
N
H
N
Cl

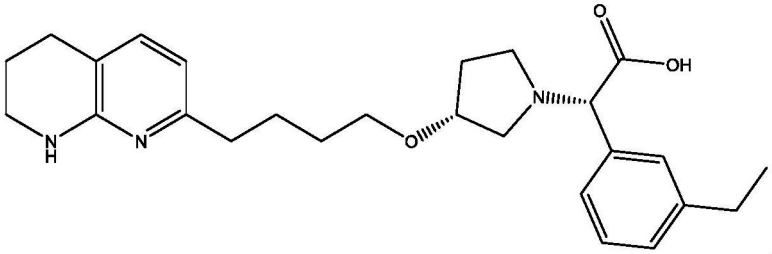
,


O
HO
O
N
N
N
H
N
F
F
F

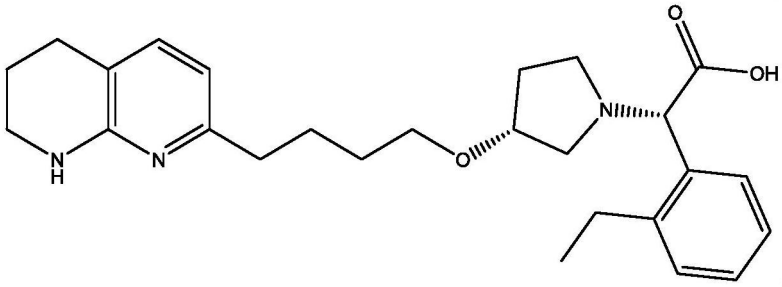
,


H
N
N
O
N
OH
O

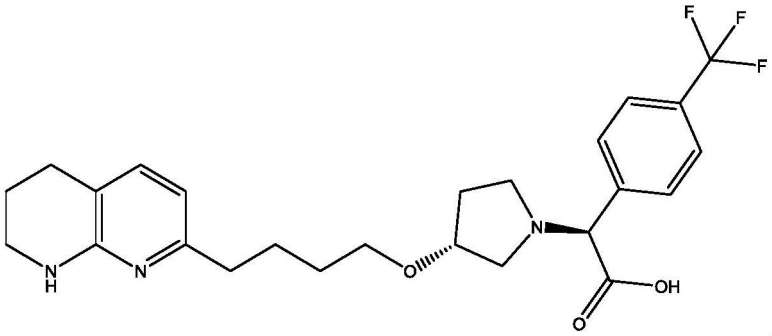
,


O
OH
N
H
N
N
O

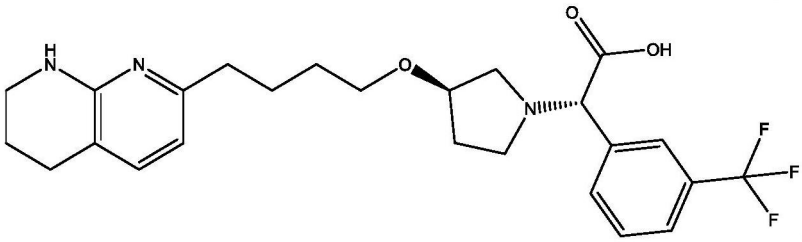
,


O
OH
N
H
N
N
O

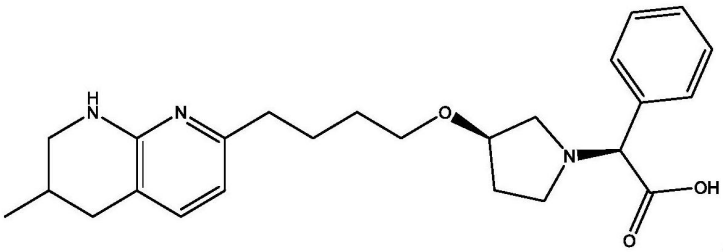
,


F
F
F
N
H
N
N
O
OH
O

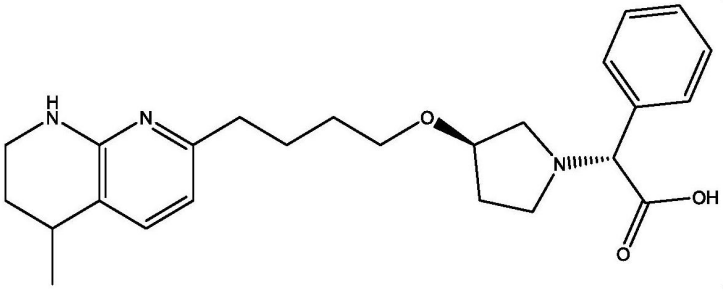
,


H
N
N
O
O
OH
N
F
F
F

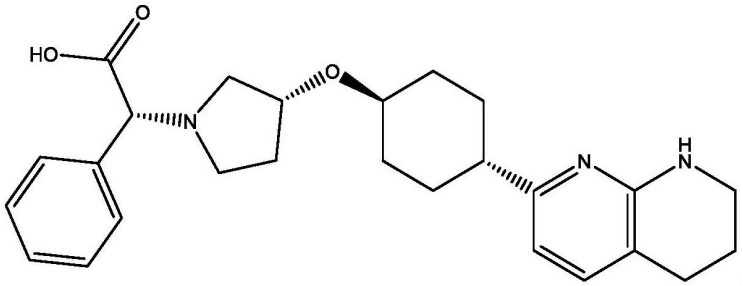
,



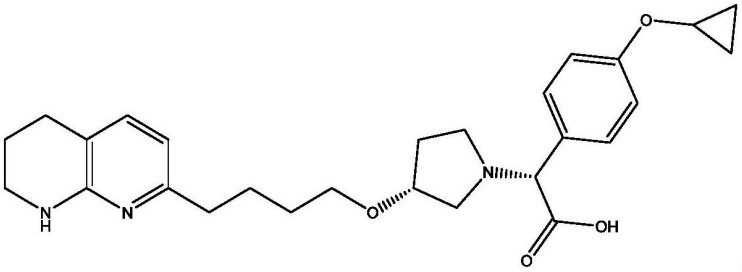
,



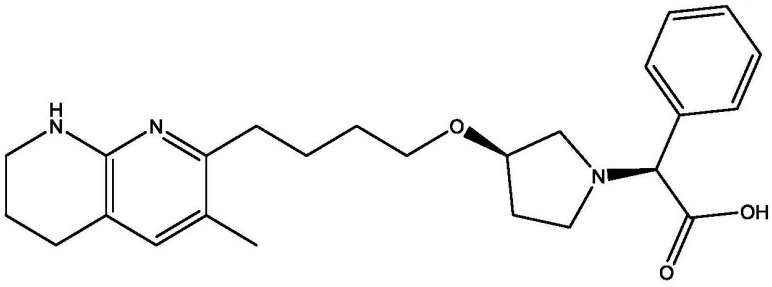
,



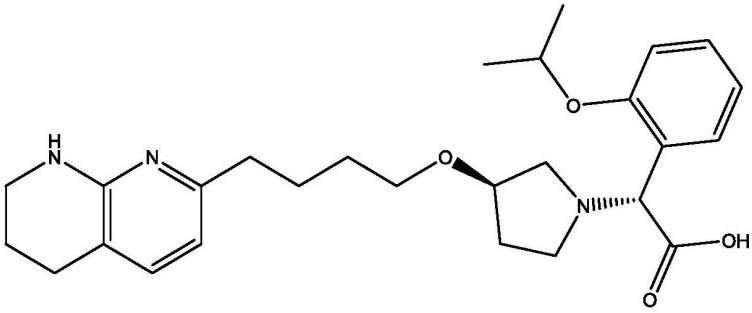
,



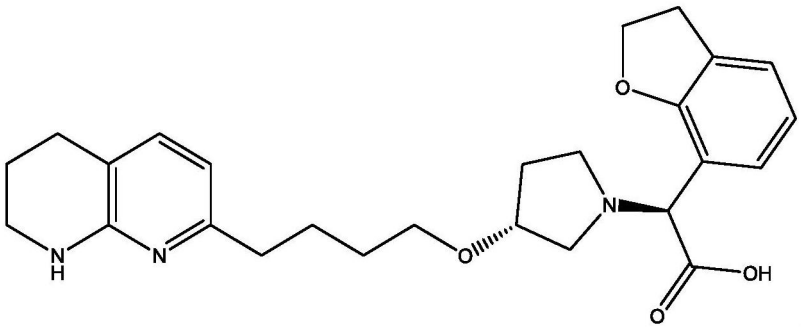
,



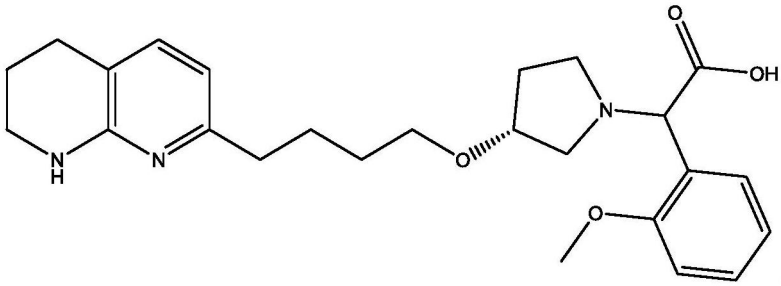
,



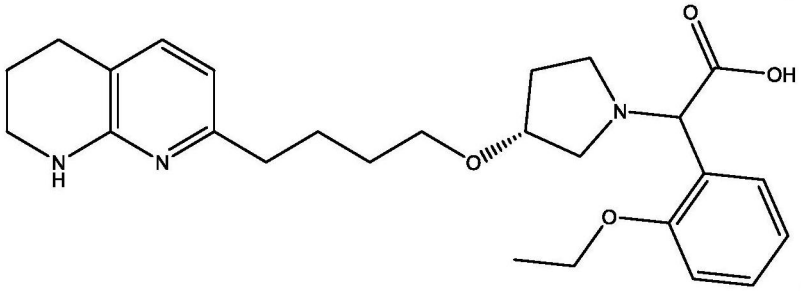
,



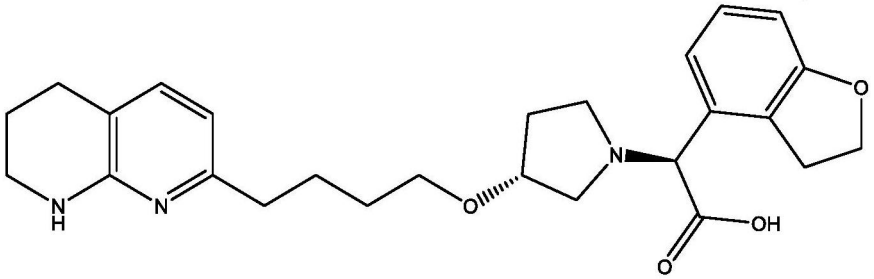
,



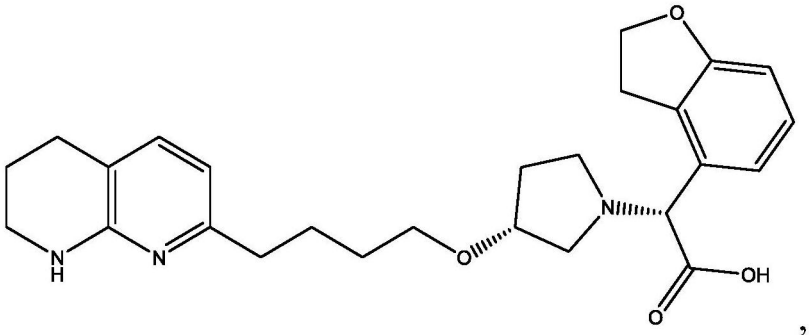
,



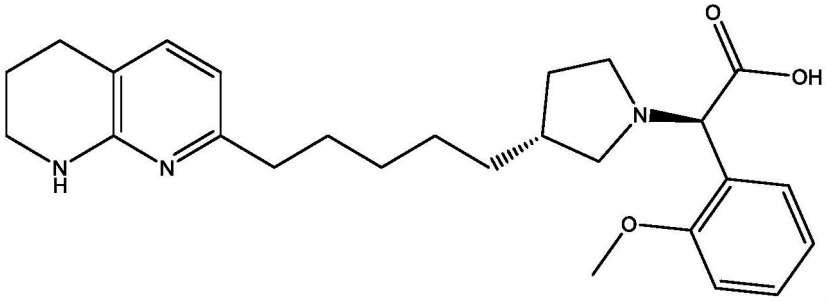
,



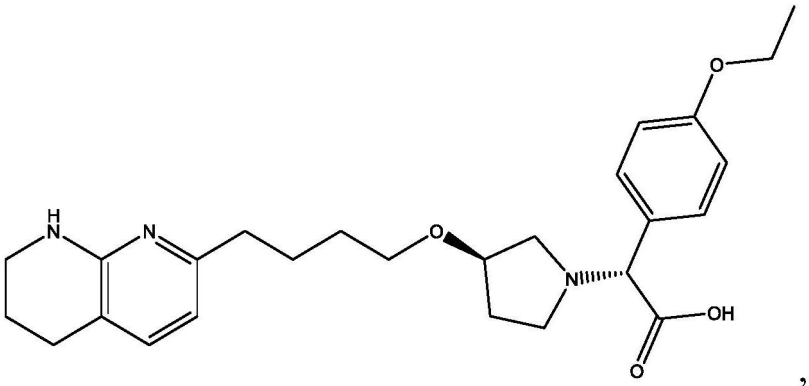
,



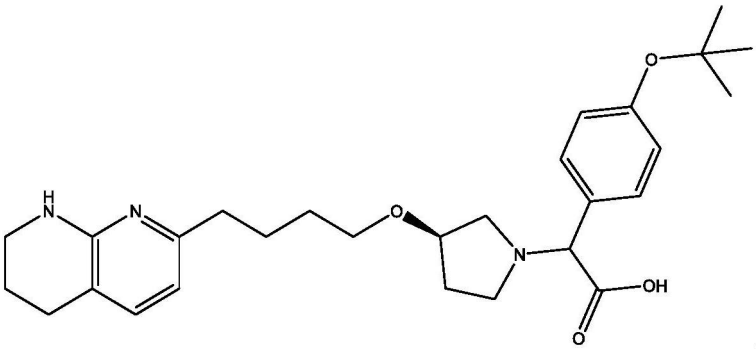
,



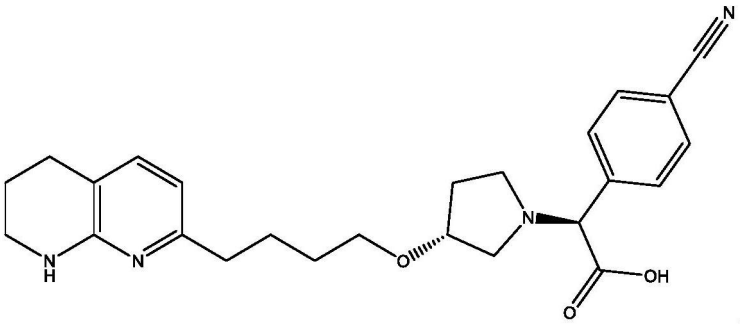
,



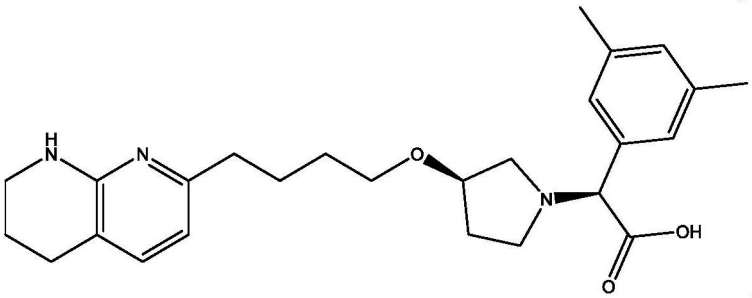
,



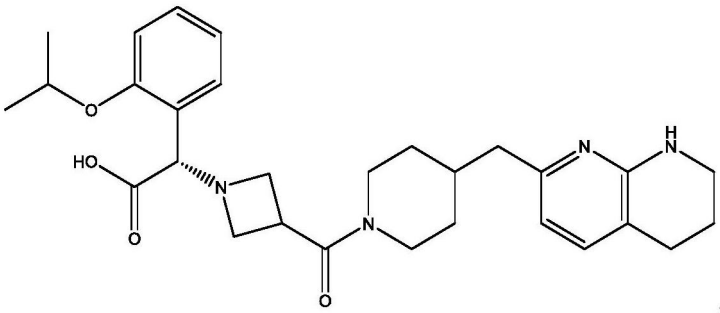
,



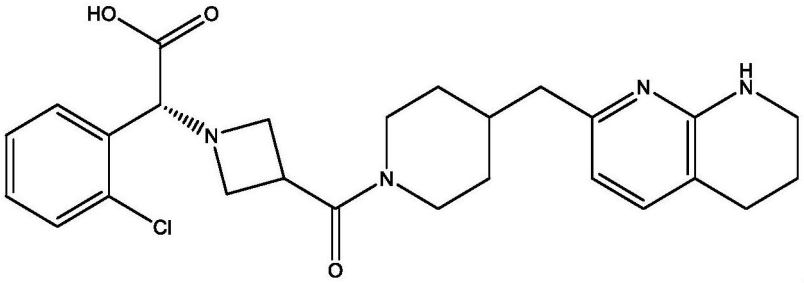
,



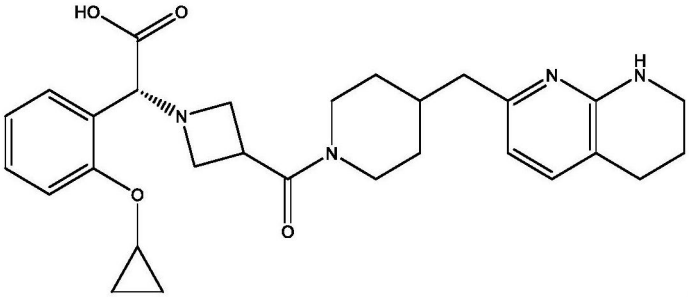
,



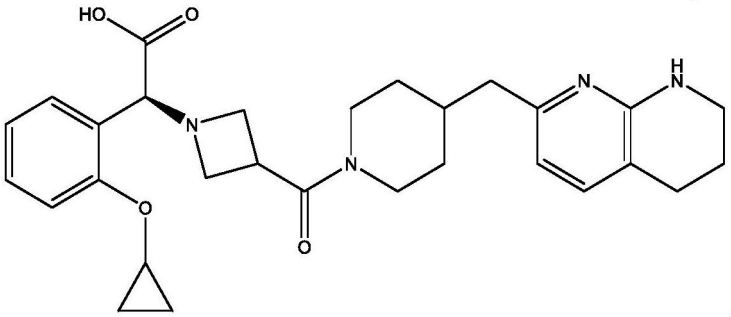
,



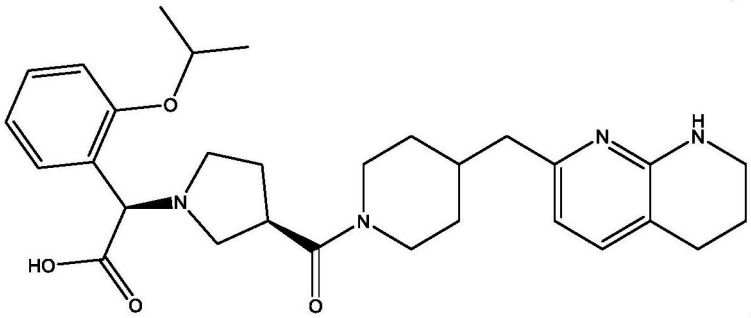
,



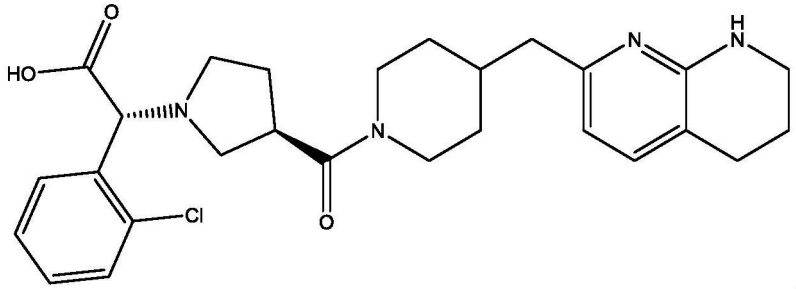
,



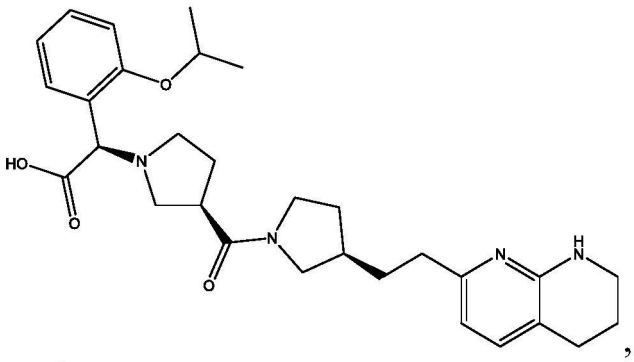
,



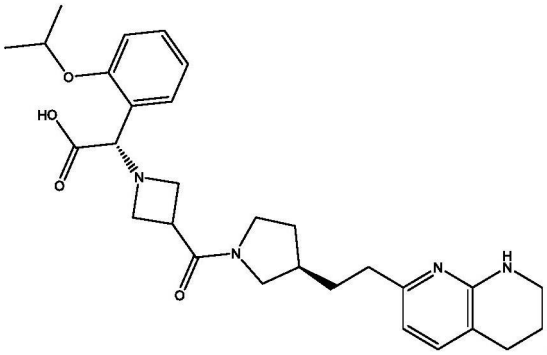
,



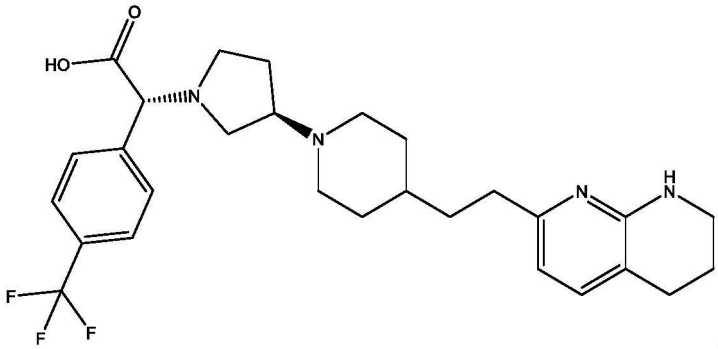
,



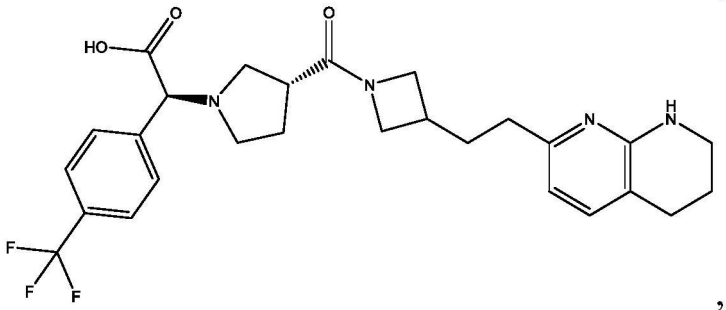
,



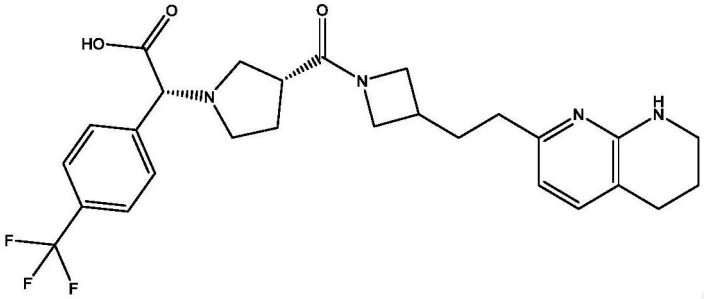
,



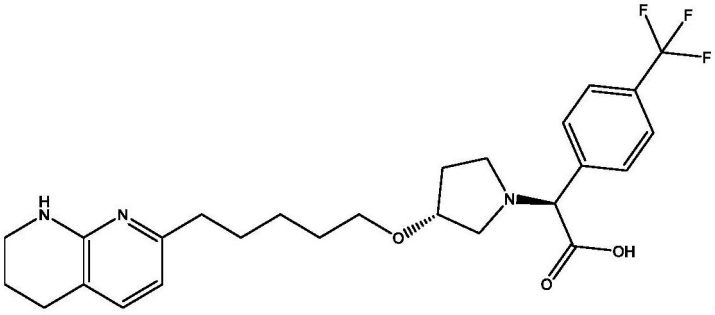
,



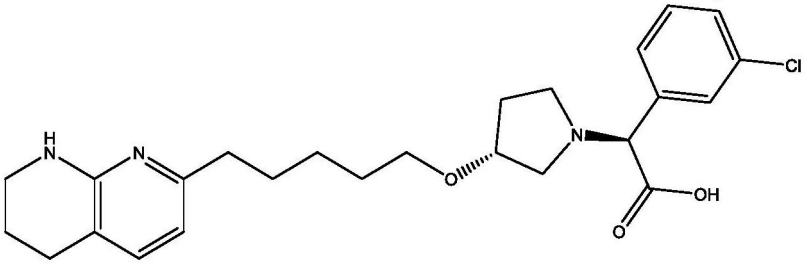
,



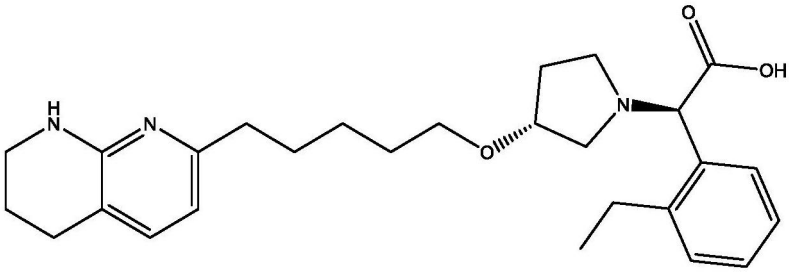
,



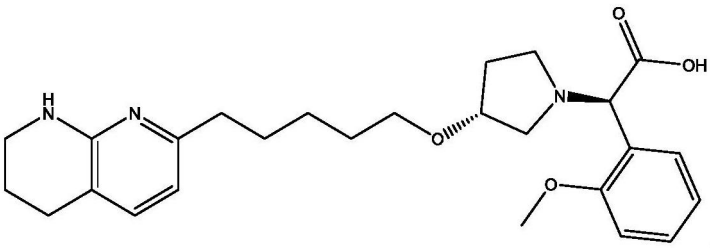
,



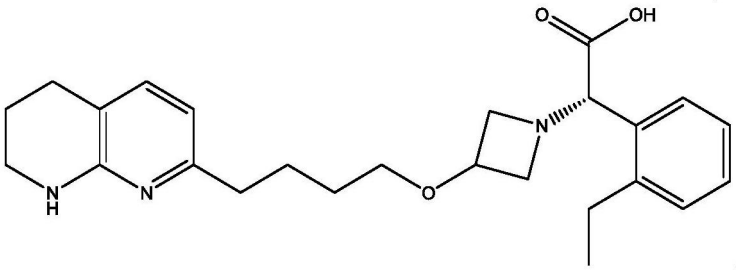
,



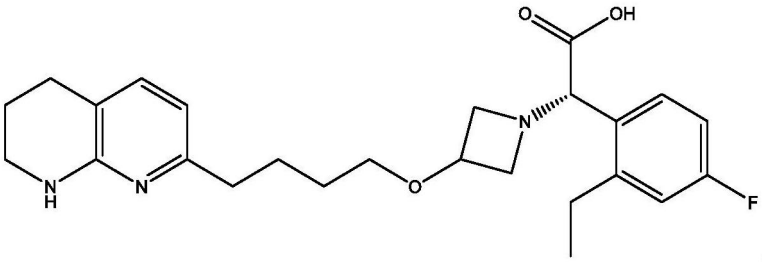
,



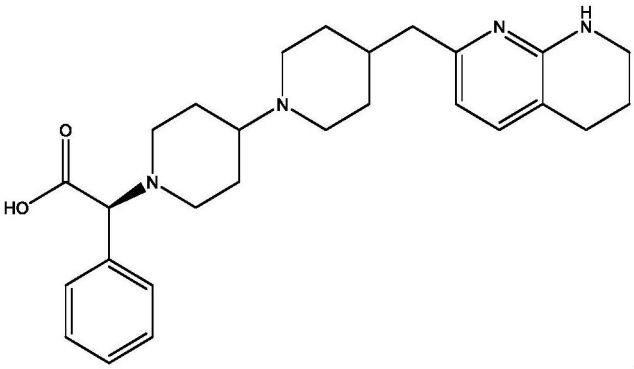
,



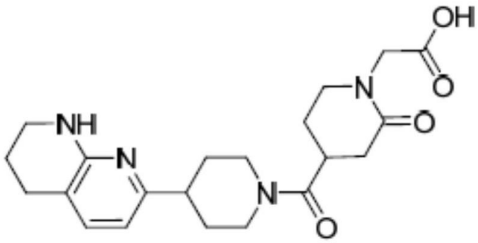
,



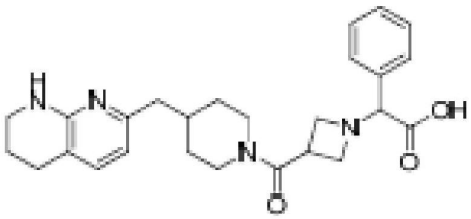
,



,



和



,或其药学上可接受的盐。

13.一种药物组合物,其包含根据权利要求1至12中任一项所述的化合物和药学上可接受的赋形剂。

14.根据权利要求1到12中任一项所述的化合物在制备用于治疗选自由以下组成的群组的疾病或病状的药物中的用途:特发性肺纤维化、糖尿病性肾病、局部区段性肾小球硬化症、慢性肾病、非酒精性脂肪性肝炎、原发性胆管炎、原发性硬化性胆管炎、实体肿瘤、血液肿瘤、器官移植、奥尔波特综合症(Alport syndrome)、间质性肺病、辐射诱导型纤维化、博来霉素(bleomycin)诱导型纤维化、石棉诱导型纤维化、流感诱导型纤维化、凝血诱导型纤维化、血管损伤诱导型纤维化、主动脉狭窄和心肌纤维化。

αvβ6整合蛋白的抑制剂

[0001] 相关申请

[0002] 本申请要求2017年2月28日提交的美国临时专利申请第62/464,693号的优先权。

背景技术

[0003] 受体的异二聚体整合蛋白家族响应于外在和内在暗示调节细胞形状和细胞对细胞外底物的粘着。

[0004] 整合蛋白信号传导控制细胞存活、细胞周期进展、细胞分化和细胞迁移。

[0005] 整合蛋白受体可专一地向细胞双向发信号,“由内向外”和“由外向内”二者。因此,其通过细胞外底物至细胞骨架的传力来介导细胞迁移并调节细胞骨架组织以达成细胞迁移期间所需的形状变化。RGD-结合整合蛋白可结合并激活TGF-β,且最近与纤维化疾病有关。

[0006] 整合蛋白在大多数人类细胞的表面上表现。其病理有助于多种人类疾病,包括血小板病症、动脉粥样硬化、癌症、骨质疏松症、纤维化、肾的糖尿病性神经病变、黄斑部退化和各种自身免疫和慢性炎症性疾病。

[0007] 早已识别整合蛋白作为药物靶标的作用且总计六种可注射整合蛋白抑制剂已由食品与药物管理局(Food and Drug Administration)批准用于治疗以下各种治疗性适应症:发炎性肠病(Entyvio®、Tysabri®)、多发性硬化症(Tysabri®)、牛皮癣(Raptiva®)和急性冠脉综合症(Reopro®、Aggrastat®、Integrilin®)。然而,明显缺失利用经口生物可利用整合蛋白抑制剂的治疗成功。

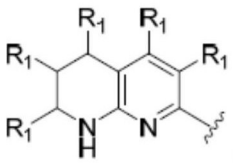
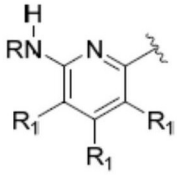
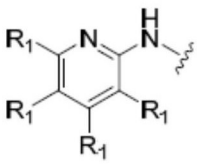
[0008] 24种已知整合蛋白异二聚体中,至少一半与炎症、纤维化、肿瘤和血管疾病有关。存在对新颖类别整合蛋白抑制剂的需求。

发明内容

[0009] 在某些实施例中,本发明涉及式I化合物:

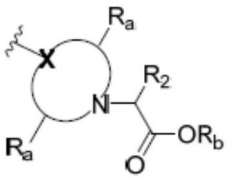
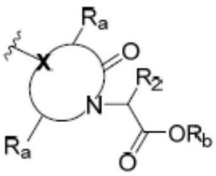
[0010] A-B-C (I)

[0011] 其中:

[0012] A为  、  或  ;

[0013] B为亚烷基、-亚烷基-(O)、-亚烷基-N(R)C(O)-、-亚烷基-(杂环基)-C(O)-、-亚烷基-C(O)N(R)-、-亚烷基-C(O)-、-亚烷基-N(R)-、-亚烷基-N(R)C(O)N(R)-、-亚烷基-N(R)SO_2-、-亚烷基-(芳基)-、-亚烷基-(杂环基)-、-亚烷基-(杂环基)-亚烷基-、-芳基-亚烷基-N(R)C(O)-、-芳基-C(O)N(R)-、-芳基-N(R)C(O)-、-(杂环基)-亚烷基-、-杂环基-亚烷基-N(R)C(O)-、-杂环基-C(O)N(R)-、-O-杂环基-、-亚烷基-O-、-杂环基-C(O)-、环亚烷基或环亚

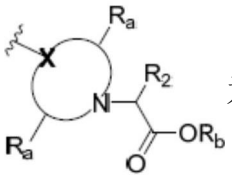
烷基-O-；

[0014] C为  或  ；

[0015] R为H、烷基或芳基；

[0016] R_1独立地为H、烷基、卤化物、烷氧基、CF_3、OH、亚烷基-OH、NO_2、-N(H)R或NH_2；

[0017] R_2为H、烷基、经取代或未经取代的芳基、经取代或未经取代的杂芳基、环烷基、-亚烷基-烷氧基、亚烷基-芳基或杂环烷基；

[0018]  为未经取代或经R_1的一个或多个实例取代的3至12元杂环亚烷基；

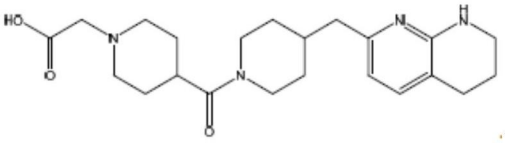
[0019] X为C(R_c)或N；

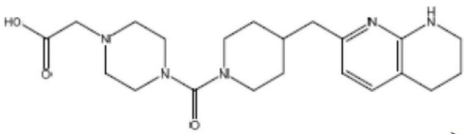
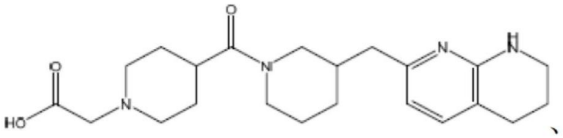
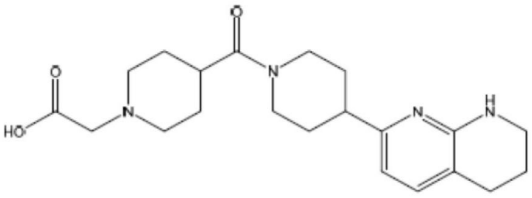
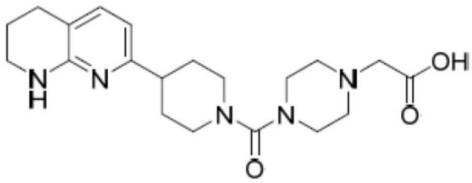
[0020] 两个R_a的实例为H，或一起形成键，或(C_1-C_4)亚烷基桥；

[0021] R_b为H或(C_1-C_6)烷基；且

[0022] R_c为H、烷基、芳基、OH或卤化物；

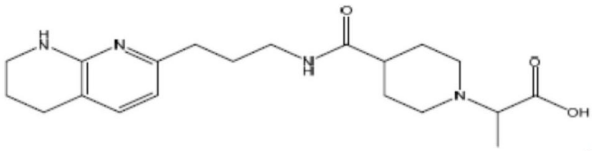
[0023] 或其药学上可接受的盐；

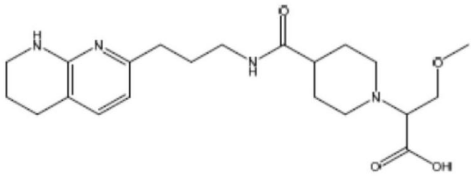
[0024] 其限制条件为所述化合物不为  、

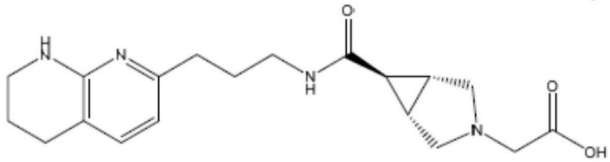
[0025]  、  、  或  。

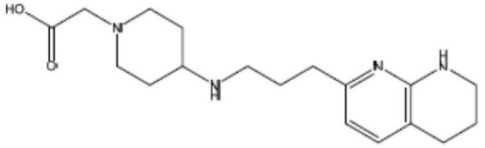
[0026] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

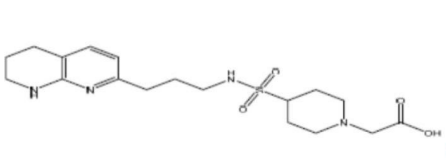
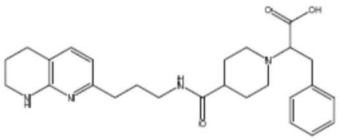
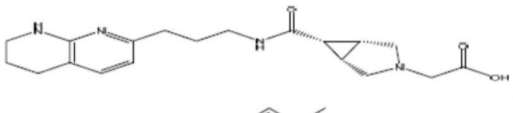
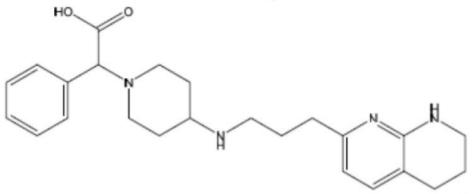
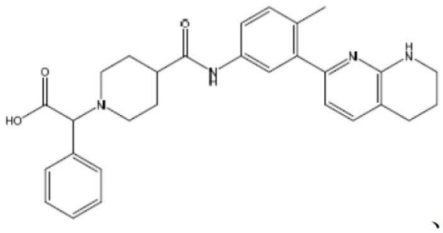
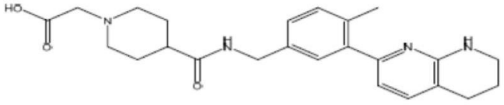
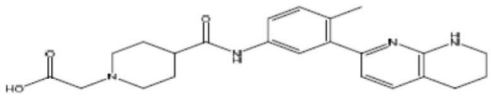
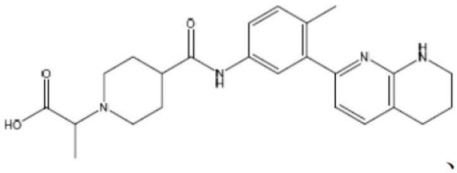
[0027]



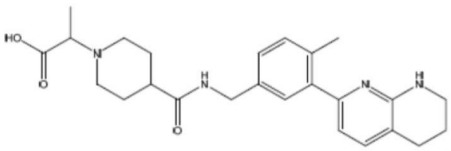
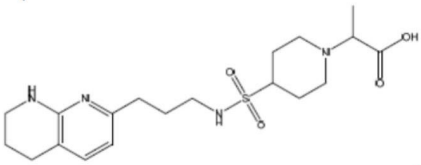
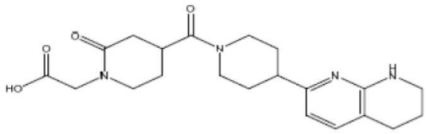
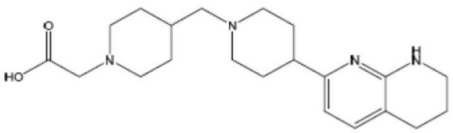
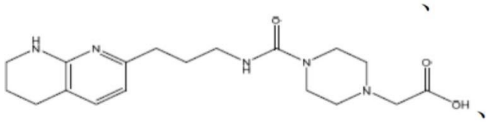
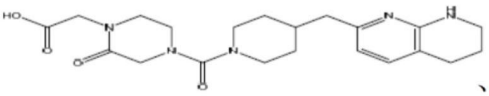
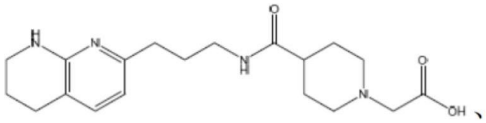
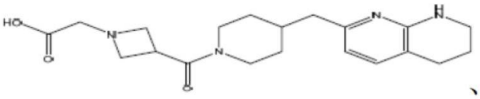
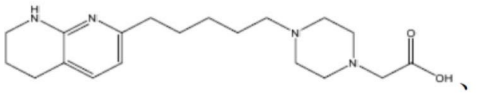




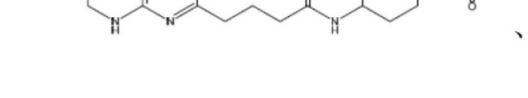



、

、

、

、

、

、

、

、

[0028]

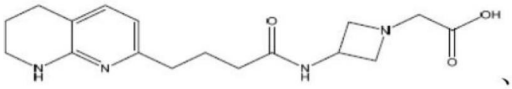

、

、

、

、

、

、

、

、

、

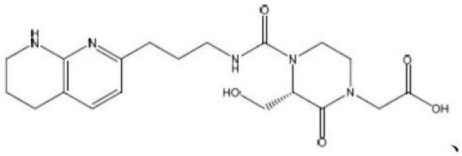
、

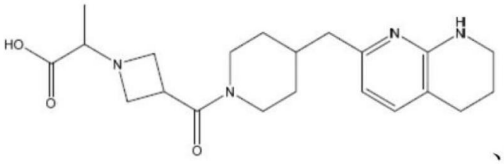
、

、

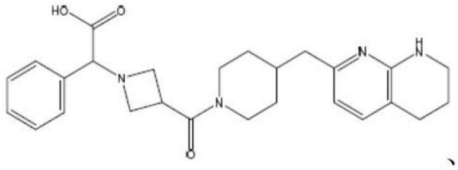
、

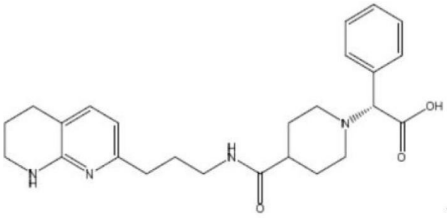
、

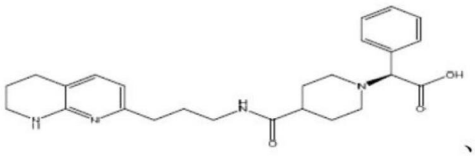


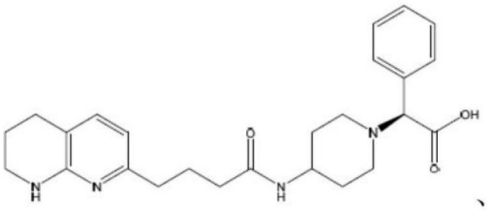


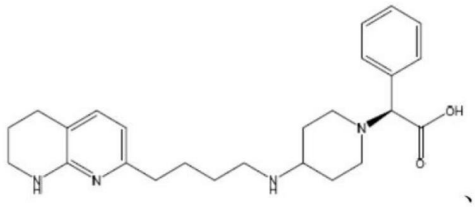




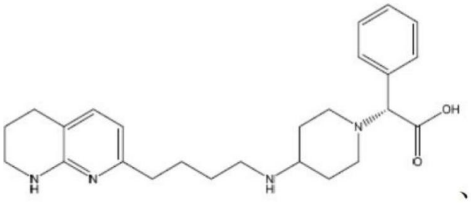


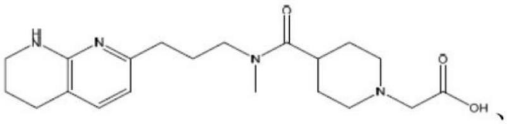


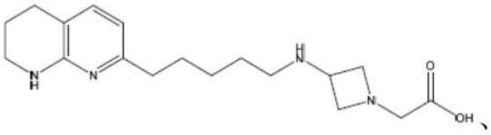


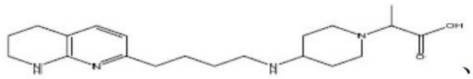


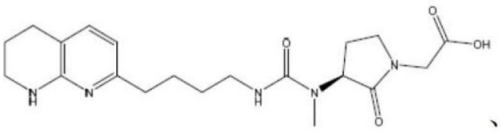
[0029]

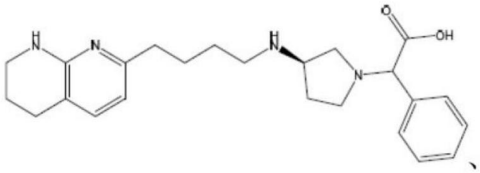


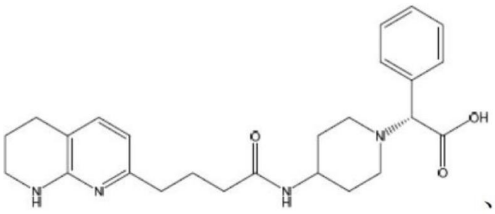


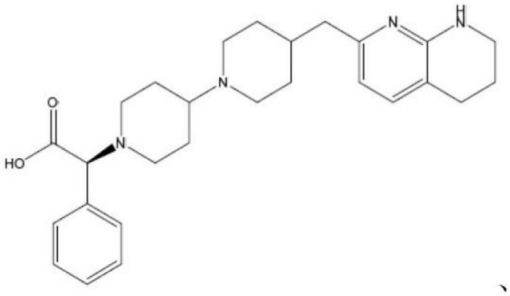




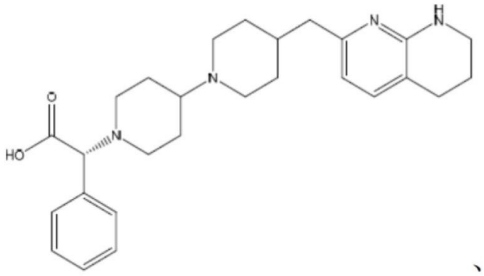


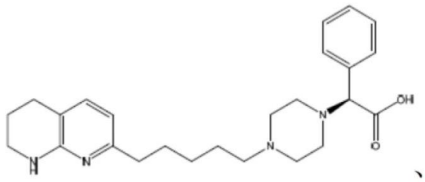


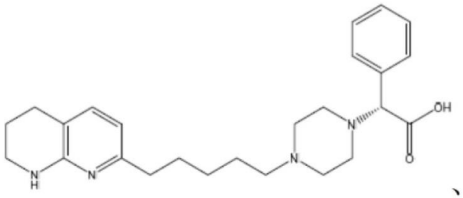


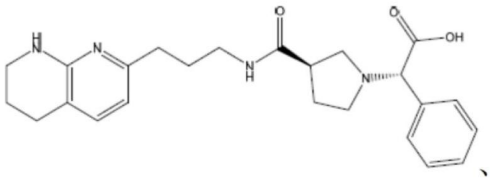


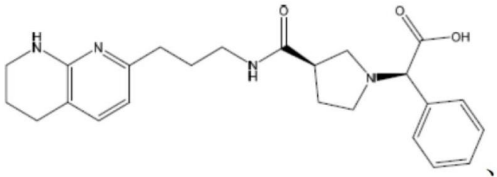
[0030]

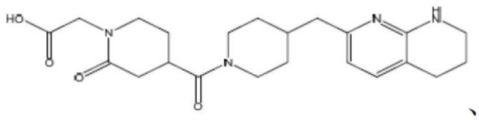


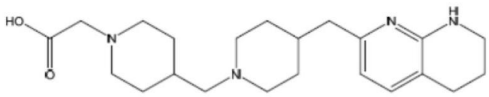


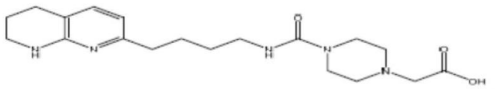


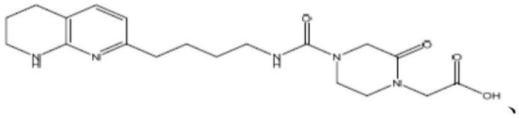


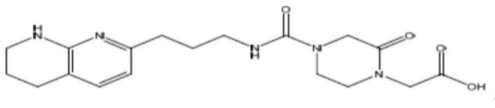


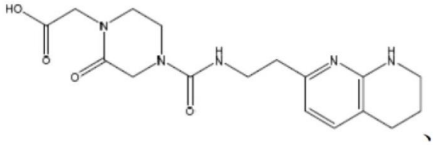


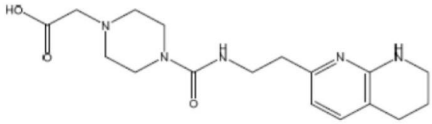


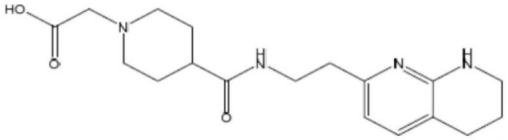


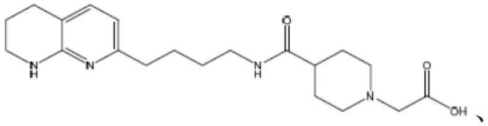


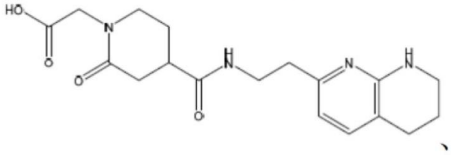


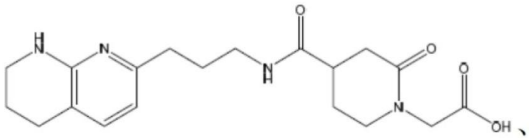


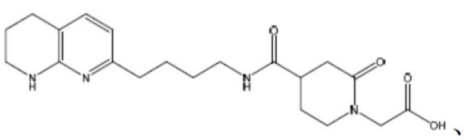


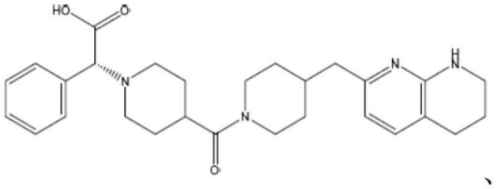


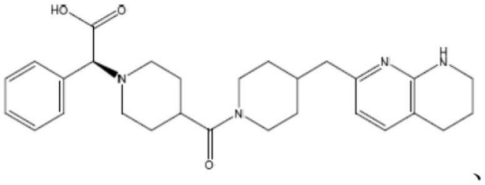


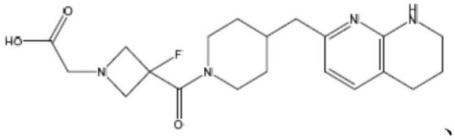


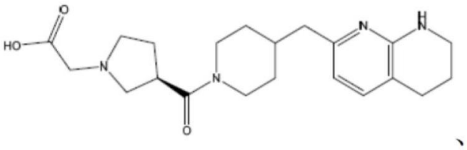


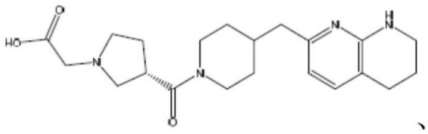


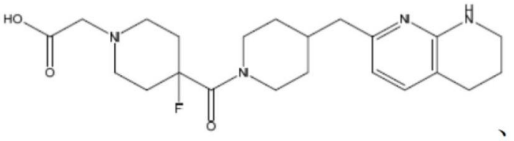


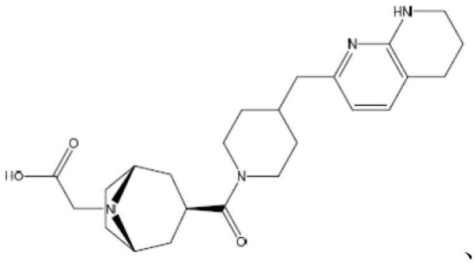


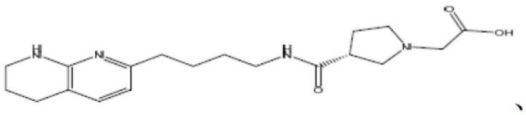




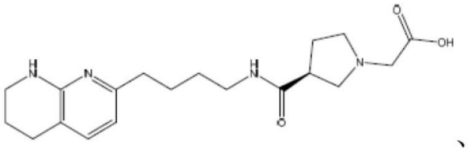


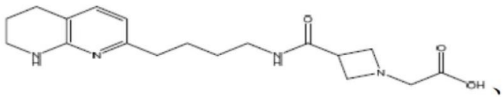


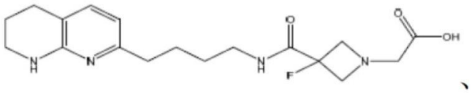


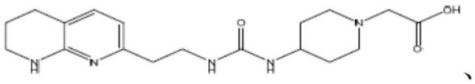


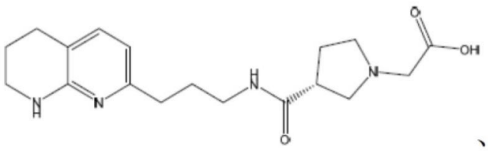
[0031]

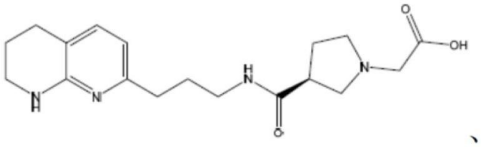


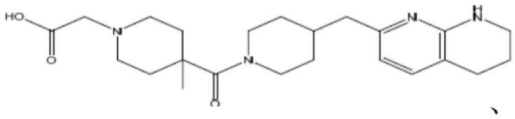


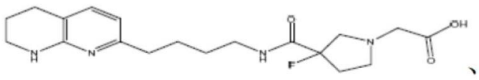


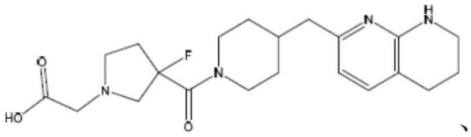


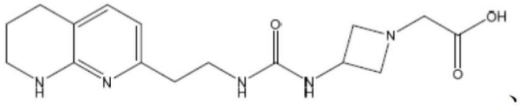


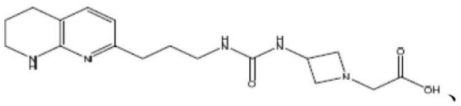


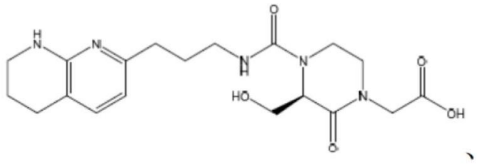


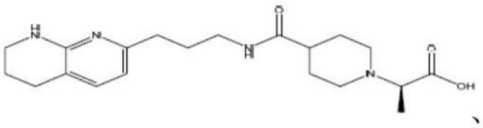


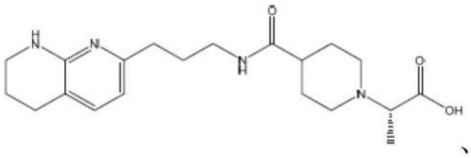


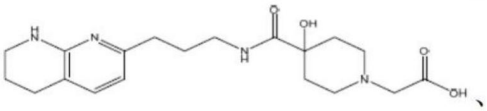


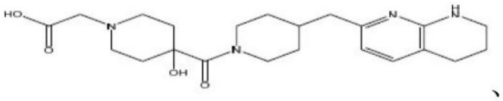


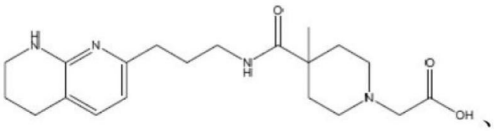


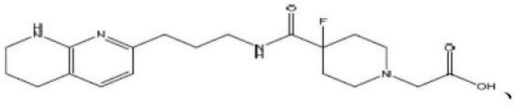


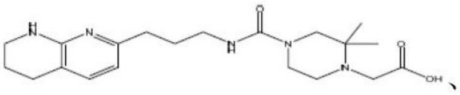


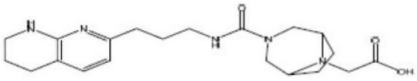


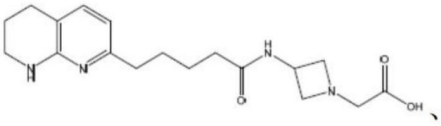


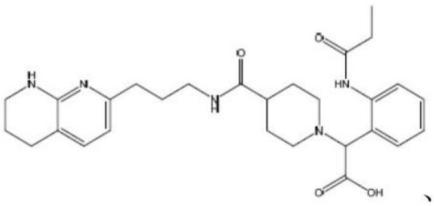




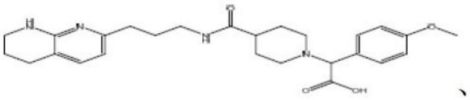


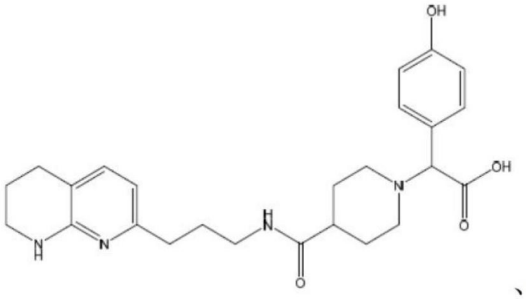


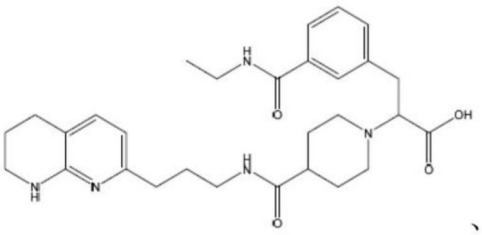


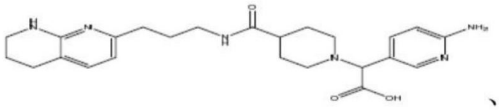


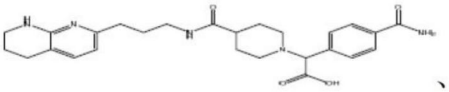
[0032]

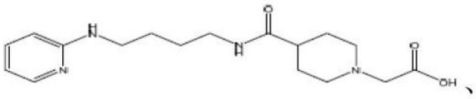


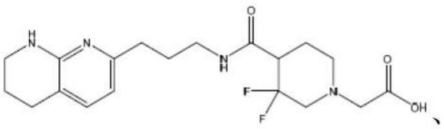


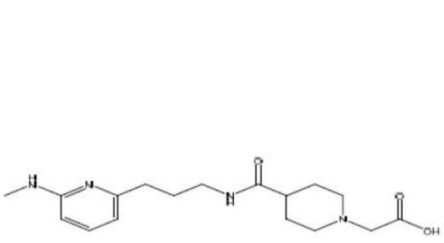
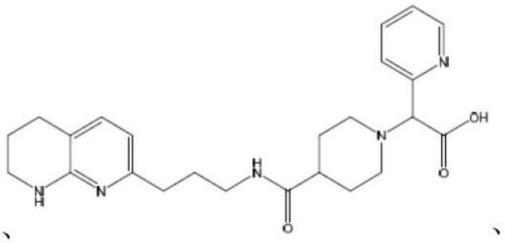
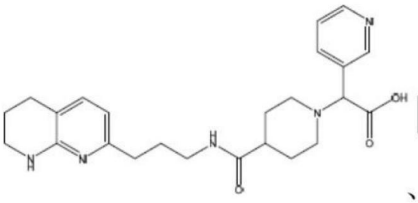
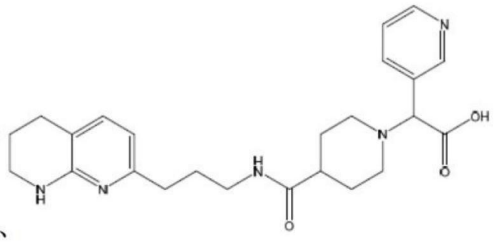
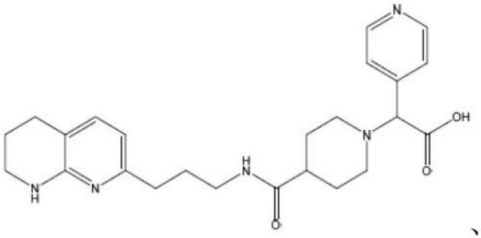
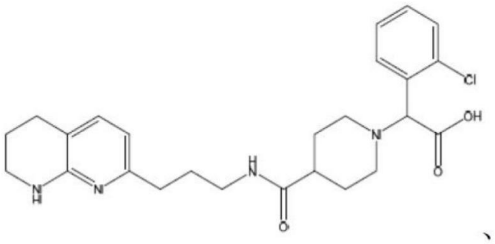




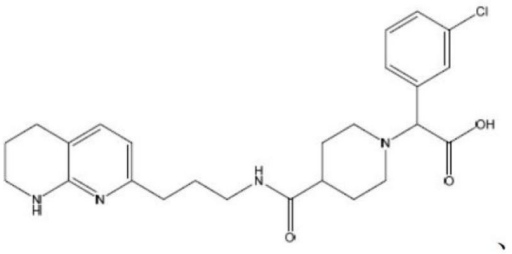
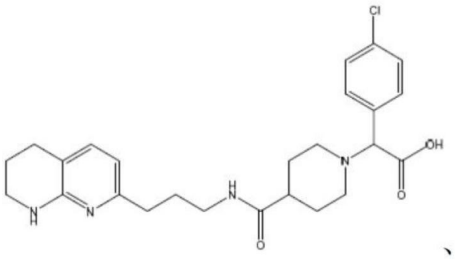
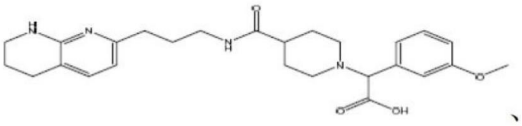
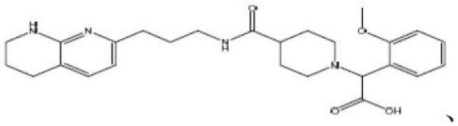
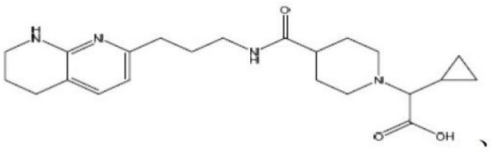
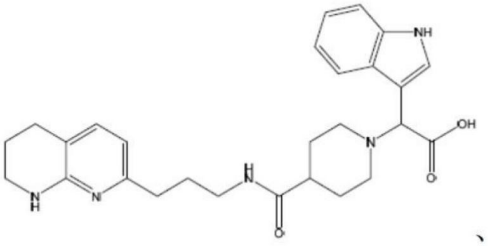
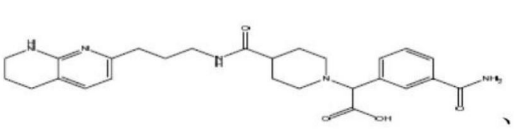
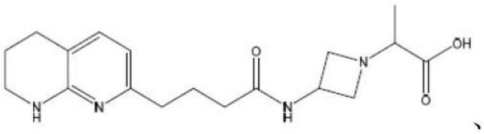




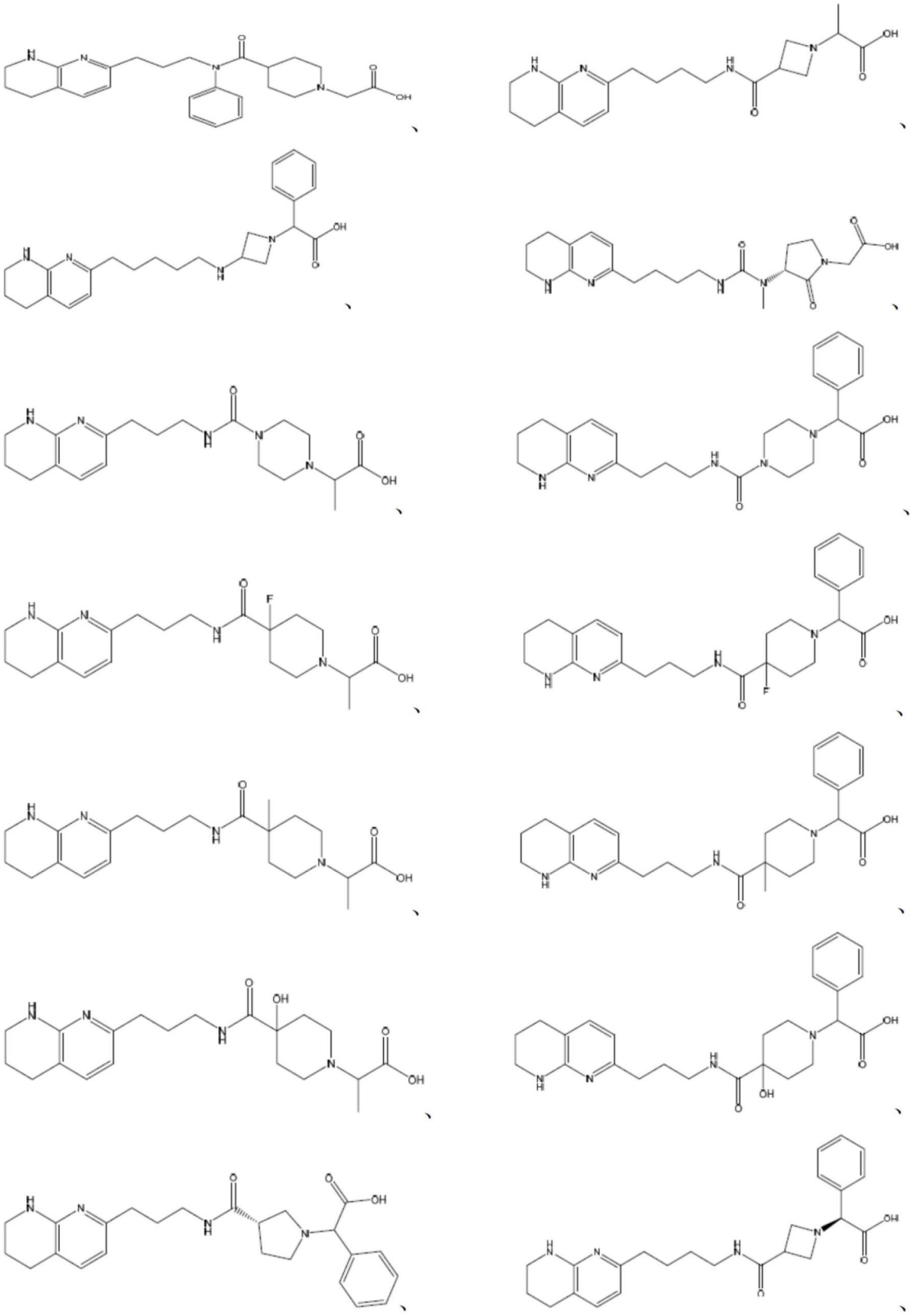


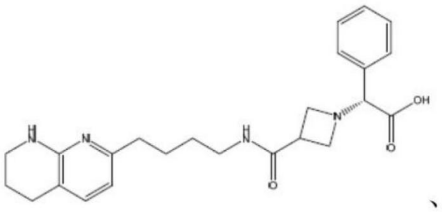







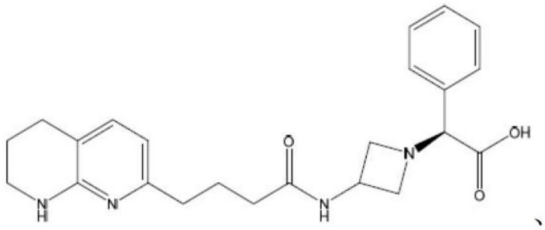
[0033]

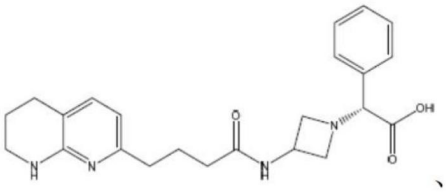









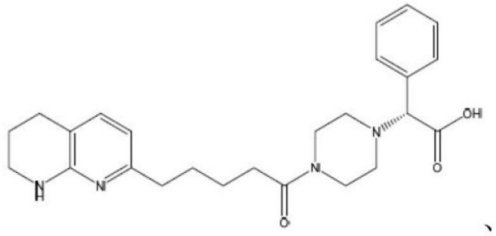
[0034]

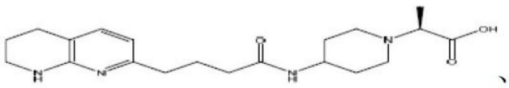


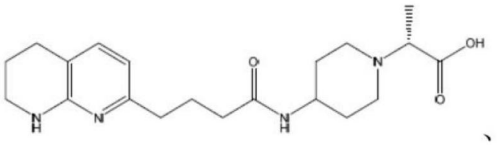




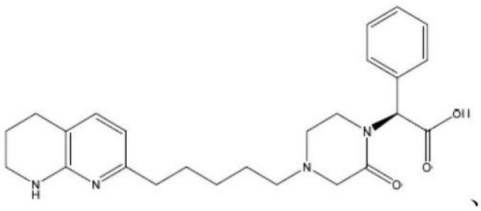


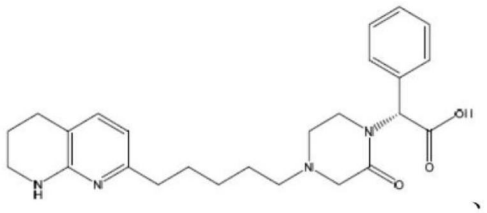


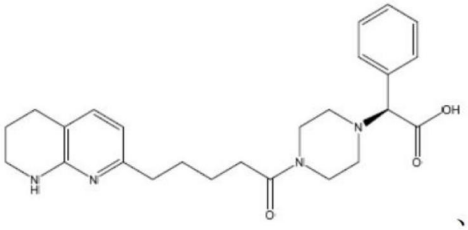


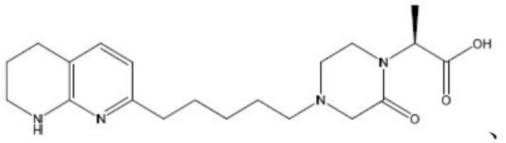


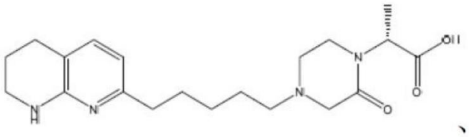
[0035]

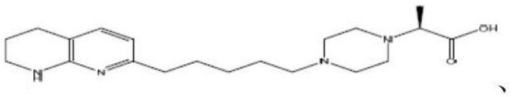


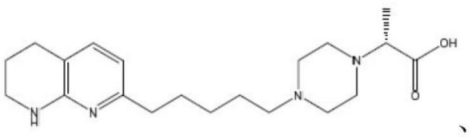


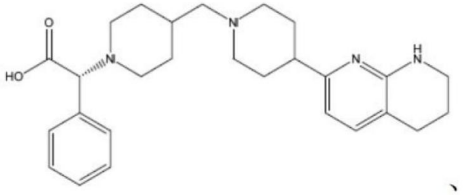


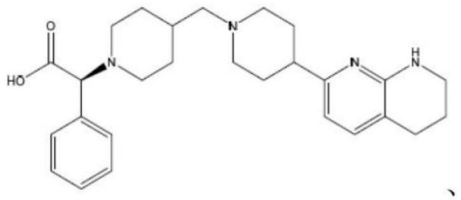


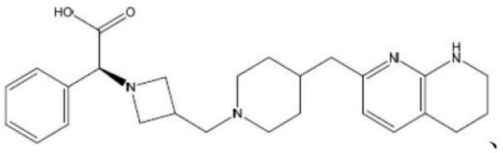


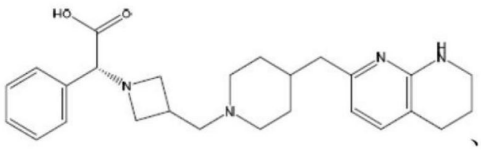
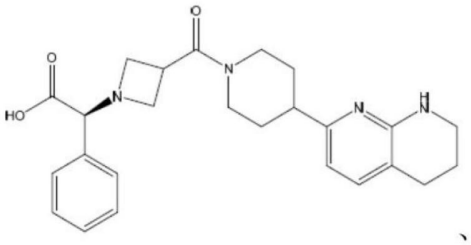
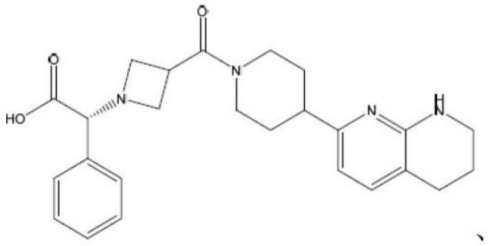
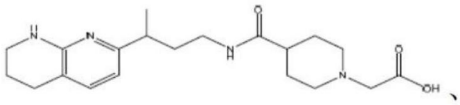
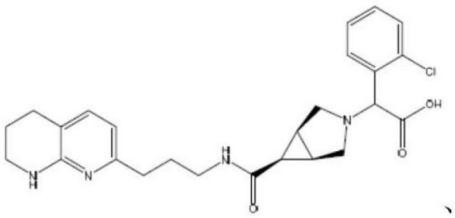
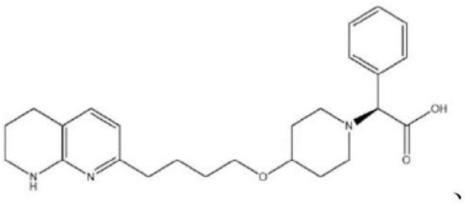
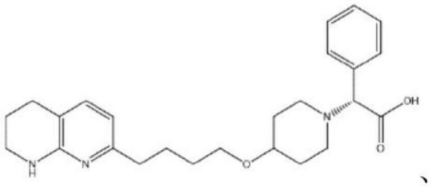
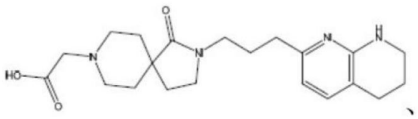
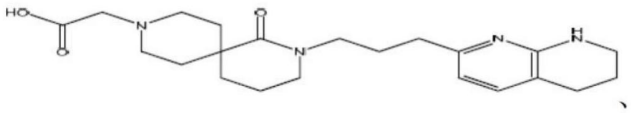
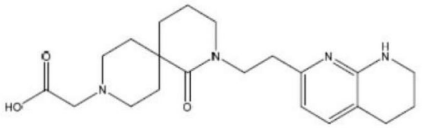
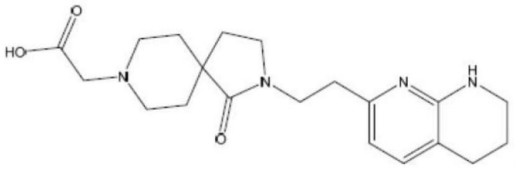






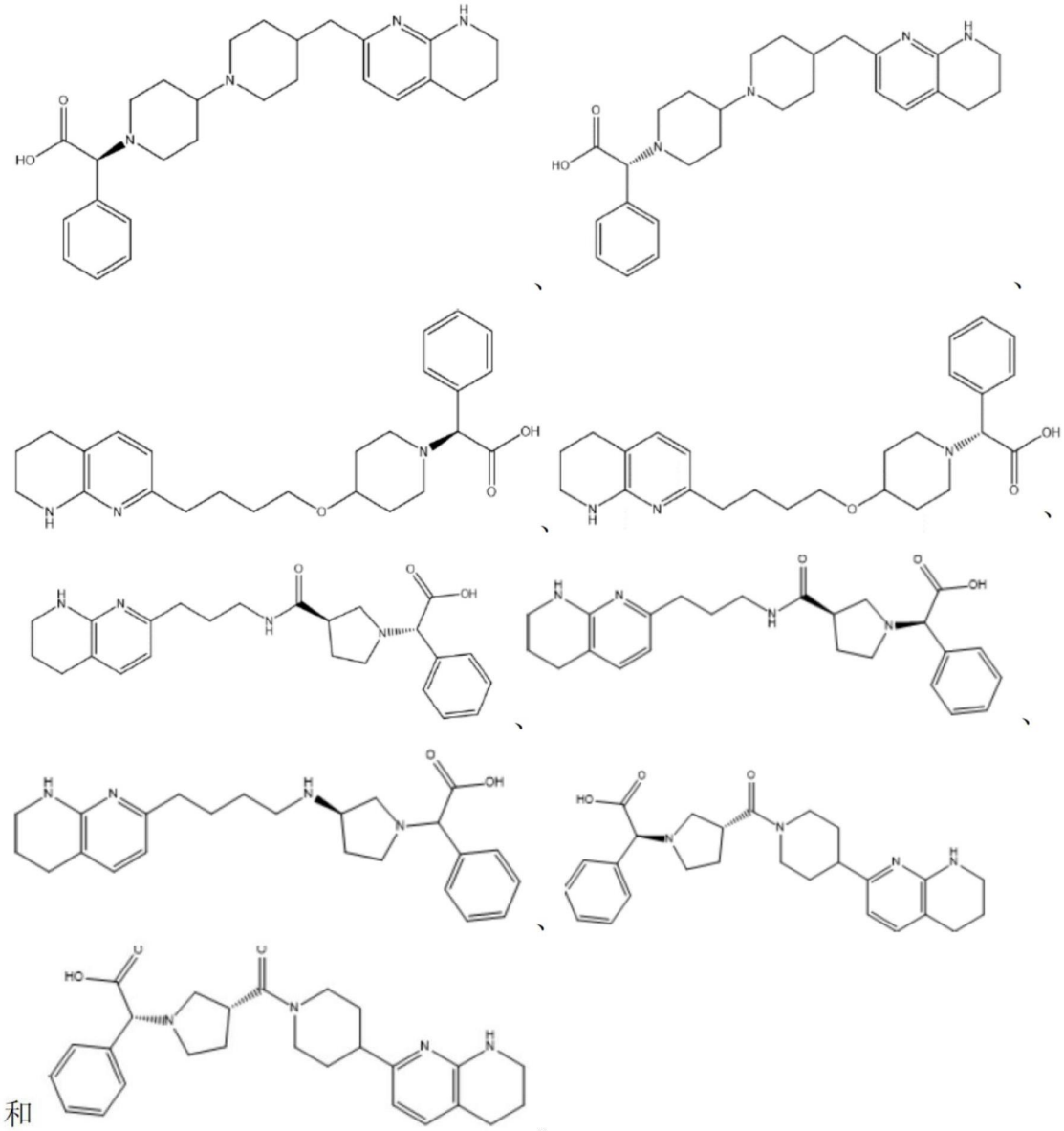




[0036]  、  、  、  、  、  、  、  、  、  和  。

[0037] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

[0038]



和 。

[0039] 在某些实施例中，本发明涉及一种治疗选自由以下组成的群组的疾病或病状的方法：特发性肺纤维化、糖尿病性肾病、局部区段性肾小球硬化症、慢性肾病、非酒精性脂肪性肝炎、原发性胆管炎、原发性硬化性胆管炎、实体肿瘤、血液肿瘤、器官移植、奥尔波特综合症(Alport syndrome)、间质性肺病、辐射诱导型纤维化、博来霉素(bleomycin)诱导型纤维化、石棉诱导型纤维化、流感诱导型纤维化、凝血诱导型纤维化、血管损伤诱导型纤维化、主动脉狭窄和心肌纤维化，所述方法包括以下步骤：对有需要的个体施用治疗上有效量的本文中所述化合物中的任一种。

附图说明

[0040] 图1描绘概述于荧光偏振检定中通过实例化合物的αvβ6整合蛋白的抑制的表格。

具体实施方式

[0041] 在某些实施例中，本发明涉及抑制αvβ6整合蛋白的化合物。在某些实施例中，所述

化合物选择性针对αvβ6整合蛋白。

[0042] 所述化合物可用于治疗特发性肺纤维化、糖尿病性肾病、局部区段性肾小球硬化症、慢性肾病、非酒精性脂肪性肝炎、原发性胆管炎、原发性硬化性胆管炎、实体肿瘤、血液肿瘤、器官移植、奥尔波特综合症、间质性肺病、辐射诱导型纤维化、博来霉素诱导型纤维化、石棉诱导型纤维化、流感诱导型纤维化、凝血诱导型纤维化、血管损伤诱导型纤维化、主动脉狭窄或心肌纤维化。

[0043] 定义

[0044] 出于方便，在进一步描述本发明之前，此处收集本说明书、实例和随附权利要求书中采用的某些术语。应根据本发明的其余部分和如由所属领域的技术人员所了解阅读这些定义。除非另有指定，否则本文中使用的所有技术和科学术语具有与一般技术人员通常理解相同的含义。

[0045] 为了更容易理解本发明，以下和整篇本说明书定义某些术语和短语。

[0046] 本文中使用冠词“一个(a/an)”是指所述冠词的语法宾语中的一个或一个以上(即，至少一个)。举例来说，“一个要素”意指一个要素或一个以上要素。

[0047] 如本文本说明书和权利要求书中所用，短语“和/或”应理解为意指如此结合的要素中的“任一个或二个”，即，在一些情况下连带存在和在其它情况下分离存在的要素。用“和/或”列出的多个要素应以相同方式解释，即，如此结合的要素中的“一个或多个”。除了由“和/或”从句特定识别的要素，可任选地存在其它要素，无论是否与特定识别的那些要素相关或无关。因此，作为非限制性实例，提及“A和/或B”，当与开放式语言(如“包括”)结合使用时可在一实施例中是指仅A(任选地包含除了B的要素)；在另一实施例中，是指仅B(任选地包含除了A的要素)；在又一实施例中，是指A与B二者(任选地包含其它要素)；等。

[0048] 如本文在本说明书和权利要求书中所用，“或”应理解为具有与如上文所定义的“和/或”相同含义。例如，当将列表中的项分离时，“或”或“和/或”应解释为包含性的，即，包含许多要素或要素列表中的至少一个，但是也包含一个以上，和，任选地包含额外未列出项。仅明确指示为相反的术语，如“仅其中的一个”或“恰其中的一个”，或，当在权利要求书中使用时，“由……组成”将指包含许多要素或要素列表中的恰一个要素。一般来说，如本文中所用，当先于排他性术语(如，“或”、“其中的一个”、“仅其中的一个”或“恰其中的一个”)时，术语“或”仅应解释为指示排他选项(即，“一个或另一个，但是非二者”)。“基本上由……组成”，当在权利要求书中使用时，应具有其如在专利法的领域中所使用的通常含义。

[0049] 如本文在本说明书和在权利要求书中所用，提及一个或多个要素的列表的短语“至少一个”应理解为意指选自要素列表中的要素中的任一个或多个的至少一个要素，但是不必需地包含要素列表内特定列出的要素各者和每个要素中的至少一个且不排除要素列表中的要素的任何组合。此定义还允许短语“至少一个”是指除了要素列表内特定识别的要素外，可任选地存在要素，无论是否与特定识别的那些要素相关或无关。因此，作为非限制性实例，“A和B中的至少一个”(或，等效地，“A或B中的至少一个”，或，等效地，“A和/或B中的至少一个”)可在一实施例中，是指至少一个，任选地包含一个以上A，不存在B(和任选地包含除了B的要素)；在另一实施例中，是指至少一个，任选地包含一个以上B，不存在A(和任选地包含除了A的要素)；在又一实施例中，是指至少一个，任选地包含一个以上A，和至少一个，任选地包含一个以上B(和任选地包含其它要素)；等。

[0050] 还应了解，除非明确相反指示，否则在本文中要求的包含超过一个步骤或行为的任何方法中，所述方法的步骤或行为的顺序不需限制叙述的方法的步骤或行为的顺序。

[0051] 在权利要求书中，以及在以上说明书中，所有过渡性短语(如“包括”、“包含”、“携带”、“具有”、“含有”、“涉及”、“持有”、“由……构成”等)将理解为开放式，即，意指包含但不限于。仅过渡性短语“由……组成”和“基本上由……组成”应分别为封闭或半封闭过渡性短语，如在美国专利局专利审查程序手册(United States Patent Office Manual of Patent Examining Procedures)，2111.03部分中所阐述。

[0052] 本发明的组合物中包含的某些化合物可呈特定几何或立体异构体形式存在。此外，本发明的聚合物也可为光学活性的。本发明涵盖包含顺式-和反式-异构体、R-和S-对映异构体、非对映异构体、(D)-异构体、(L)-异构体、其外消旋混合物和落于本发明的范围内的其其它混合物的所有这些化合物。其它不对称碳原子可存在于取代基中，如烷基。所有这些异构体，以及其混合物意图包含于本发明内。

[0053] 如果，例如，本发明的化合物的特定对映异构体为所需的，则其可通过不对称合成或通过手性助剂衍生来制备，其中将所得非对映异构混合物分离并将辅助基团裂解以提供纯的所需对映异构体。或者，其中分子含有碱性官能团(如氨基)或酸性官能团(如羧基)，利用适宜光学活性酸或碱形成非对映异构盐，接着将因此由分级结晶或所属领域中熟知的色谱方法形成的非对映异构体解析，和随后回收纯的对映异构体。

[0054] 本文中描绘的结构还意指包含仅在于存在一个或多个同位素浓化原子的不同化合物。例如，通过用氘或氚置换氢或用^{13}C-或^{14}C-浓化碳置换碳制备的化合物在本发明的范围内。

[0055] 如本文中所用，术语“前药”涵盖在生理条件下，转化成治疗上活化剂的化合物。制备前药的常见方法包括在生理条件下水解以显示所需分子的选定部分。在其它实施例中，通过宿主动物的酵素活性转化所述前药。

[0056] 如本文中所用，短语“药学上可接受的赋形剂”或“药学上可接受的载剂”意指药学上可接受的物质、组合物或媒剂(如液体或固体填料、稀释剂、赋形剂、溶剂或封装物质)，其涉及将目标化学品自身体的一个器官或部分运送或递送至身体的另一器官或部分。在与调配物的其它成分兼容、对患者无害且基本上无热原性的意义下，各载剂必须为“可接受的”。可用作药学上可接受的载剂的物质的一些实例包括：(1)糖，如乳糖、葡萄糖和蔗糖；(2)淀粉，如玉米淀粉和马铃薯淀粉；(3)纤维素和其衍生物，如羧甲基纤维素钠、乙基纤维素和乙酸纤维素；(4)粉末黄蓍胶；(5)麦芽；(6)明胶；(7)滑石；(8)赋形剂，如可可油和栓剂蜡；(9)油，如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油；(10)二醇，如丙二醇；(11)多元醇，如甘油、山梨醇、甘露醇和聚乙二醇；(12)酯，如油酸乙酯和月桂酸乙酯；(13)琼脂；(14)缓冲剂，如氢氧化镁和氢氧化铝；(15)藻酸；(16)无热原水；(17)等渗盐水；(18)林格氏溶液(Ringer’s solution)；(19)乙醇；(20)磷酸盐缓冲液；和(21)在医药调配物中采用的其它无毒兼容性物质。在某些实施例中，本发明的药物组合物为无热原性，即，当向患者施用时，不引起显著温度上升。

[0057] 术语“药学上可接受的盐”是指化合物的相对无毒、无机和有机酸加成盐。这些盐可在化合物的最终单离和纯化期间原位制备或通过呈其游离碱形式的纯化化合物与适宜有机或无机酸单独反应和单离由此形成的盐制备。代表性盐包括氢溴酸盐、盐酸盐、硫酸

盐、硫酸氢盐、磷酸盐、硝酸盐、乙酸盐、戊酸盐、油酸盐、棕榈酸盐、硬脂酸盐、月桂酸盐、苯甲酸盐、乳酸盐、甲苯磺酸盐、柠檬酸盐、马来酸盐、富马酸盐、琥珀酸盐、酒石酸盐、萘酸盐、甲磺酸盐、葡庚糖酸盐、乳糖醛酸盐和月桂基磺酸盐等。(参见，例如，Berge等人，(1977)“Pharmaceutical Salts”，J.Pharm.Sci.66:1-19。)

[0058] 在其它情况下，可用于本发明的方法中的化合物可含有一个或多个酸性官能团，和因此能与药学上可接受的碱形成药学上可接受的盐。在这些实例中，术语“药学上可接受的盐”是指化合物的相对无毒、无机和有机碱加成盐。这些盐可同样地在化合物的最终单离和纯化期间原位制备，或通过呈其游离酸形式的纯化化合物与适宜碱(如药学上可接受的金属阳离子的氢氧化物、碳酸盐或碳酸氢盐)、与氨、或与药学上可接受的有机伯、仲或叔胺单独反应制备。代表性碱或碱土盐包括锂、钠、钾、钙、镁和铝盐等。可用于形成碱加成盐的代表性有机胺包括乙胺、二乙胺、乙二胺、乙醇胺、二乙醇胺、哌嗪等(参见例如，Berge等人，见上)。

[0059] 相对于治疗中的使用来说的化合物的“治疗上有效量”(或“有效量”)，是指制剂中的化合物的量，当作为所需剂量方案的部分施用(给哺乳动物，优选地人类)时，其根据待治疗的病症或病状的临床上可接受的标准或化妆目的，例如，以适用于任何医学治疗的合理利益/风险比减轻症状、改善病状或减慢疾病状况的发作。

[0060] 术语“预防性或治疗性”治疗经技术认可和包含向宿主施用一种或多种目标组合物。如果其在非所需病状(例如，宿主动物的疾病或其它非所需状态)的临床表现之前施用，则所述治疗为预防性，(即，其保护宿主免于发展非所需病状)，然而如果其于非所需病状的表现后施用，则所述治疗为治疗性，(即，其意图减弱、改善或稳定存在的非所需病状或其副作用)。

[0061] 术语“患者”是指需要特定治疗的哺乳动物。在某些实施例中，患者为灵长类、犬科、猫科或马科动物。在某些实施例中，患者为人类。

[0062] 脂族链包括以下定义的烷基类、烯基类和炔基类。将直链脂族链限制为未分支碳链部分。如本文中所用，术语“脂族基团”是指直链、分支链或环状脂族烃基且包含饱和和不饱和脂族基团，如烷基、烯基或炔基。

[0063] “烷基”是指具有指定碳原子数目，或如果未制定规格，则至多30个碳原子的完全饱和环状或无环、分支或未分支碳链部分。例如，1至8个碳原子的烷基是指如甲基、乙基、丙基、丁基、戊基、己基、庚基和辛基的基团，和为这些基团的位置异构体的那些基团。10至30个碳原子的烷基包括癸基、十一烷基、十二烷基、十三烷基、十四烷基、十五烷基、十六烷基、十七烷基、十八烷基、十九烷基、二十烷基、二十一烷基、二十二烷基、二十三烷基和二十四烷基。在某些实施例中，直链或分支链烷基于其主链中具有30个或更少个碳原子(例如，针对直链C_1-C_{30}，针对分支链C_3-C_{30})，和更优选地20个或更少。烷基可经取代或未经取代。

[0064] 如本文中所用，术语“亚烷基”是指具有指定碳数目(例如，2至12个碳原子)的烷基，其在其最长碳链上含有连接至化合物的其余部分的两个连接点。亚烷基的非限制性实例包括亚甲基-(CH_2)-、亚乙基-(CH_2CH_2)-、亚正丙基-$(CH_2CH_2CH_2)$-、亚异丙基-$(CH_2CH(CH_3))$-等。亚烷基可为环状或无环、分支或未分支碳链基团，和可任选地经一个或多个取代基取代。

[0065] “环烷基”意指各者具有3至12个碳原子的单环或双环或桥接或螺环，或多环饱和

碳环状环。同样地，优选环烷基于其环结构中具有3至10个碳原子，和更优选地于环结构中具有3至6个碳。环烷基可经取代或未经取代。

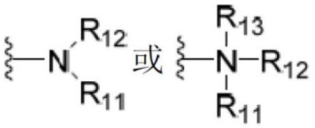
[0066] 除非碳的数目另有指定，否则如本文中所用，“低碳数烷基”意指如上所定义的烷基，但是在其主链结构中具有1至10个碳，更优选地1至6个碳原子，如甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基和叔丁基。同样地，“低碳数烯基”和“低碳数炔基”具有类似链长度。整篇申请中，优选烷基为低碳数烷基。在某些实施例中，本文中指定的取代基如烷基为低碳数烷基。

[0067] “烯基”是指具有指定碳原子数目，或如果不限制指定碳原子的数目，则至多26个碳原子；且在基团中具有一个或多个双键的任何环状或无环、分支或未分支不饱和碳链基团。6至26个碳原子的烯基例示如下：呈其各种异构体形式的己烯基、庚烯基、辛烯基、壬烯基、癸烯基、十一烯基、十二烯基、十三烯基、十四烯基、十五烯基、十六烯基、十七烯基、十八烯基、十九烯基、二十烯基、二十一烯基、二十二烯基、二十三烯基和二十四烯基，其中不饱和键可位于基团中任何位置且可具有关于双键的(Z)或(E)构型。

[0068] “炔基”是指烯基范围的烃基部分，但是在部分中具有一个或多个三键。

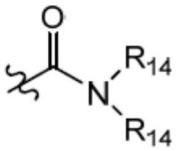
[0069] 术语“烷硫基”是指如上所定义的烷基，其具有其上连接的硫基。在某些实施例中，“烷硫基”基团由-(S)-烷基、-(S)-烯基、-(S)-炔基和-(S)-$(CH_2)_m$-R^1中的一个表示，其中m和R^1定义如下。代表性烷硫基包括甲硫基、乙硫基等。如本文中所用，术语“烷氧基(alkoxyl/alkoxy)”是指如上所定义的烷基，其具有其上连接的氧部分。代表性烷氧基包括甲氧基、乙氧基、丙氧基、叔丁氧基等。“醚”为通过氧共价连接的两个烃。因此，使烷基成为醚的烷基的取代为或类似于烷氧基，如可由-O-烷基、-O-烯基、-O-炔基、-O-$(CH_2)_m$-R_{10}中的一个表示，其中m和R_{10}描述于下。

[0070] 术语“胺”和“氨基”经技术认可且是指未经取代和经取代的胺二者，例如，可由下式表示的部分：

[0071] 

[0072] 其中R_{11}、R_{12}和R_{13}各者独立地表示氢、烷基、烯基、-$(CH_2)_m$-R_{10}，或R_{11}和R_{12}与其所连接的N原子一起形成于环结构中具有4至8个原子的杂环；R_{10}表示烯基、芳基、环烷基、环烯基、杂环基或多环基；且m为0或1至8范围中的整数。在某些实施例中，R_{11}或R_{12}中仅一者可为羰基，例如，R_{11}、R_{12}和氮一起不形成酰亚胺。在甚至更多特定实施例中，R_{11}和R_{12}(和任选地R_{13})各者独立地表示氢、烷基、烯基或-$(CH_2)_m$-R_{10}。因此，如本文中所用，术语“烷基胺”意指如上所定义的氨基，其具有其上连接的经取代或未经取代的烷基，即，R_{11}和R_{12}中的至少一个为烷基。在某些实施例中，氨基或烷基胺为碱性，意指其具有pK_a>7.00的共轭酸，即，这些官能团的质子化形式具有相对于水约7.00以上的pK_a。

[0073] 如本文中所用，术语“酰胺”是指基团

[0074] 

[0075] 其中各R_{14}独立地表示氢或烃基，或两个R_{14}与其所连接的N原子一起形成于环结构中具有4至8个原子的杂环。

[0076] 如本文中所用，术语“芳基”包括3至12元经取代或未经取代的单环芳族基团，其中环的各原子为碳(即，碳环芳基)或其中一个或多个原子为杂原子(即，杂芳基)。优选地，芳基包括5-至12-元环，更优选地6-至10-元环。术语“芳基”还包括具有两个或多个环状环的多环环系，其中两个或多个碳为两个相邻环共享，其中环中的至少一个为芳族，例如，另一环状环可为环烷基、环烯基、环炔基、芳基、杂芳基和/或杂环基。碳环芳基包括苯、萘、菲、苯酚、苯胺等。杂芳基包括经取代或未经取代的芳族3-至12-元环结构，更优选地5-至12-元环，更优选地5-至10-元环，所述环的环结构包含1至4个杂原子。杂芳基包括(例如)吡咯、呋喃、噻吩、咪唑、噁唑、噻唑、三唑、吡唑、吡啶、吡嗪和嘧啶等。芳基和杂芳基可为单环、双环或多环。

[0077] 如本文中所用，术语“卤基”、“卤化物”或“卤素”意指卤素和包括(例如)且不限于呈放射性和非放射性形式二者的氟、氯、溴、碘等。在一优选实施例中，卤基选自由氟、氯和溴组成的群组。

[0078] 术语“杂环基(heterocyclyl/heterocyclic group)”是指3-至12-元环结构，更优选地5-至12-元环，更优选地5-至10-元环，所述环的环结构包含1至4个杂原子。杂环可为单环、双环、螺环或多环。杂环基包括(例如)噻吩、噻蒽、呋喃、哌喃、异苯并呋喃、色烯、氧杂蒽、吩噁噻、吡咯、咪唑、吡唑、异噻唑、异噁唑、吡啶、吡嗪、嘧啶、哒嗪、吲嗪、异吲哚、吲哚、吲唑、嘌呤、喹嗪、异喹啉、喹啉、酞嗪、萘啶、喹噁啉、喹唑啉、噌啉、喋啶、咔唑、咔啉、菲啶、吖啶、菲咯啉、吩嗪、吩吡嗪、吩噻嗪、呋咱、吩噁嗪、吡咯烷、氧戊环、硫戊环、噁唑、哌啶、哌嗪、吗啉、内酯、内酰胺(如氮杂环丁酮和吡咯烷酮)、磺内酰胺、磺内酯等。杂环状环可在一个或多个位置处经如上所述的这些取代基取代，例如，卤素、烷基、芳烷基、烯基、炔基、环烷基、羟基、氨基、硝基、氢硫基、亚氨基、酰胺基、磷酸酯、膦酸酯、亚膦酸酯、羰基、羧基、硅基、氨磺酰基、亚硫酰基、醚、烷硫基、磺酰基、酮、醛、酯、杂环基、芳族或杂芳族基团、$-CF_3$、-CN等。

[0079] 术语“羰基”经技术认可且包括可由下式表示的这些基团：

[0080] 

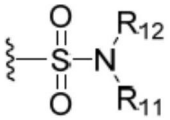
[0081] 其中X’为键或表示氧或硫，且R_{15}表示氢、烷基、烯基、$-(CH_2)_m-R_{10}$或药学上可接受的盐，R_{16}表示氢、烷基、烯基或$-(CH_2)_m-R_{10}$，其中m和R_{10}如以上所定义。在X’为氧且R_{15}或R_{16}不为氢的情况下，所述式表示“酯”。在X’为氧，且R_{15}如上所定义的情况下，本文中所述基团称作羧基，和确切地说当R_{15}为氢时，所述式表示“羧酸”。在X’为氧，且R_{16}为氢的情况下，所述式表示“甲酸酯”。一般来说，在上式的氧原子经硫置换的情况下，所述式表示“硫代羰基”。在X’为硫且R_{15}或R_{16}不为氢的情况下，所述式表示“硫酯”基。在X’为硫且R_{15}为氢的情况下，所述式表示“硫代羧酸”基。在X’为硫且R_{16}为氢的情况下，所述式表示“硫代甲酸酯”基。另一方面，在X’为键，且R_{15}不为氢的情况下，上式表示“酮”基。在X’为键且R_{15}为氢的情况下，上式表示“醛”基。

[0082] 如本文中所用，术语“经取代”预期包括有机化合物的所有容许取代基。在一广泛

方面中，所述容许取代基包括有机化合物的无环和环状、分支和未分支、碳环和杂环、芳族和非芳族取代基。说明性取代基包括(例如)本文中上述的那些。所述容许取代基可为一个或多个和对于适宜有机化合物为相同或不同。出于本发明的目的，如氮的杂原子可具有满足杂原子的化学价的本文中所述有机化合物的氢取代基和/或任何容许取代基。不意图以任何方式通过有机化合物的容许取代基限制本发明。应了解“取代”或“经……取代”包括隐性限制性条款，此取代是根据经取代原子和取代基的容许价，且所述取代导致稳定化合物，例如，其不自发经历转化(如通过重排、环化、消除等)。

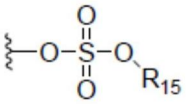
[0083] 如本文中所用，术语“硝基”意指-NO_2；术语“卤素”指示-F、-Cl、-Br或-I；术语“硫氢基”意指-SH；术语“羟基”意指-OH；术语“磺酰基”意指-SO_2-；术语“迭氮基”意指-N_3；术语“氰基”意指-CN；术语“异氰酸根基”意指-NCO；术语“硫氰酸根基”意指-SCN；术语“异硫氰酸根基”意指-NCS；和术语“氰酸根基”意指-OCN。

[0084] 术语“氨磺酰基”经技术认可且包括可由下式表示的基团：

[0085] 

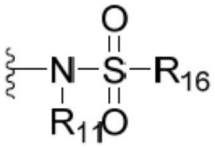
[0086] 其中R_{11}和R_{12}如上所定义。

[0087] 术语“硫酸酯”经技术认可且包括可由下式表示的基团：

[0088] 

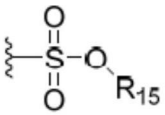
[0089] 其中R_{15}如上所定义。

[0090] 术语“磺酰胺”经技术认可且包括可由下式表示的基团：

[0091] 

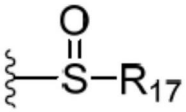
[0092] 其中R_{11}和R_{16}如上所定义。

[0093] 术语“磺酸酯”经技术认可且包括可由下式表示的基团：

[0094] 

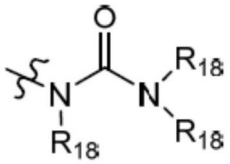
[0095] 其中R_{54}为电子对、氢、烷基、环烷基或芳基。

[0096] 如本文中所用，术语“亚砜基”或“亚磺酰基”是指可由下式表示的基团：

[0097] 

[0098] 其中R_{17}选自由以下组成的群组：氢、烷基、烯基、炔基、环烷基、杂环基、芳烷基或芳基。

[0099] 术语“脲”经技术认可且可由以下通式表示：

[0100] 

[0101] 其中各R_{18}独立地表示氢或烃基(如烷基),或任何出现的R_{18}与另一个原子和介入原子一起形成于环结构中具有4至8个原子的杂环。

[0102] 如本文中所用,各表述(例如,烷基、m、n等)的定义,当其于任何结构中出现超过一次时,意图独立于其于相同结构中别处的定义。

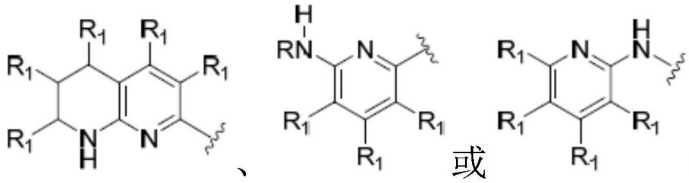
[0103] 出于本发明的目的,根据元素周期表(CAS版本)、化学和物理手册(Handbook of Chemistry and Physics),第67版,1986-87,内封面识别化学元素。

[0104] 本发明的示例性化合物

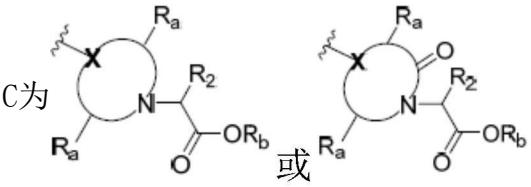
[0105] 在某些实施例中,本发明涉及式I化合物:

[0106] A-B-C (I)

[0107] 其中:

[0108] A为  ;

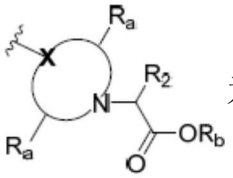
[0109] B为亚烷基、-亚烷基-(O)、-亚烷基-N(R)C(O)-、-亚烷基-(杂环基)-C(O)-、-亚烷基-C(O)N(R)-、-亚烷基-C(O)-、-亚烷基-N(R)-、-亚烷基-N(R)C(O)N(R)-、-亚烷基-N(R)SO_2-、-亚烷基-(芳基)-、-亚烷基-(杂环基)-、-亚烷基-(杂环基)-亚烷基-、-芳基-亚烷基-N(R)C(O)-、-芳基-C(O)N(R)-、-芳基-N(R)C(O)-、-(杂环基)-亚烷基-、-杂环基-亚烷基-N(R)C(O)-、-杂环基-C(O)N(R)-、-O-杂环基-、-亚烷基-O-、-杂环基-C(O)-、环亚烷基或环亚烷基-O-;

[0110] C为  ;

[0111] R为H、烷基或芳基;

[0112] R_1独立地为H、烷基、卤化物、烷氧基、CF_3、OH、NO_2、-N(H)R或NH_2;

[0113] R_2为H、烷基、经取代或未经取代的芳基、经取代或未经取代的杂芳基、环烷基、-亚烷基-烷氧基、亚烷基-芳基或杂环烷基;

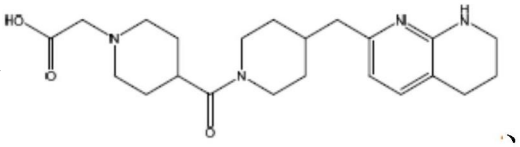
[0114]  为未经取代或经R_1的一个或多个实例取代的3至12元杂环亚烷基;

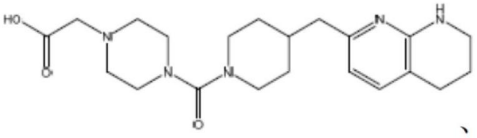
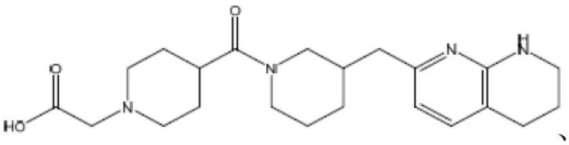
[0115] X为C(R_c)或N;

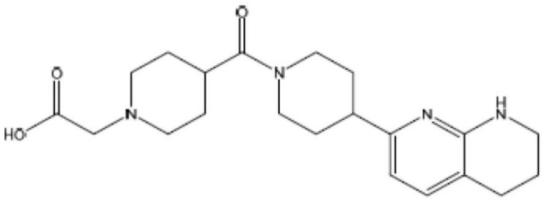
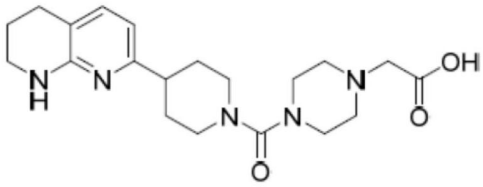
[0116] 两个R_a的实例为H,或一起形成键,或(C_1-C_4)亚烷基桥;R_6为H或(C_1-C_6)烷基;且

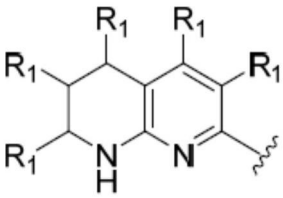
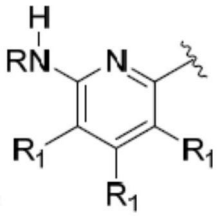
[0117] R_c为H、烷基、芳基、OH或卤化物；

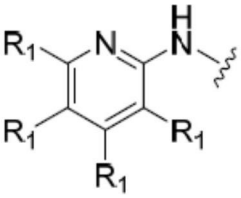
[0118] 或其药学上可接受的盐；

[0119] 其限制条件为所述化合物不为  、

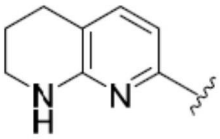
 、  、

[0120]  或 

[0121] 在某些实施例中，本发明涉及上述化合物中的任一种，其中A为  在某些实施例中，本发明涉及上述化合物中的任一种，其中A为  。

在某些实施例中，本发明涉及上述化合物中的任一种，其中A为  。

在某些实施例中，本发明涉及上述化合物中的任一种，其中A为 。

 。

[0122] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1独立地为H、烷基、卤化物、烷氧基、CF_3、OH、亚烷基-OH、NO_2、-N(H)R或NH_2。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1独立地烷基、卤化物、烷氧基、CF_3、OH、亚烷基-OH、NO_2或NH_2。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1为烷基、卤化物、OMe、OH、亚烷基-OH或NH_2。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为烷基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为甲基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为亚烷基-OH。在

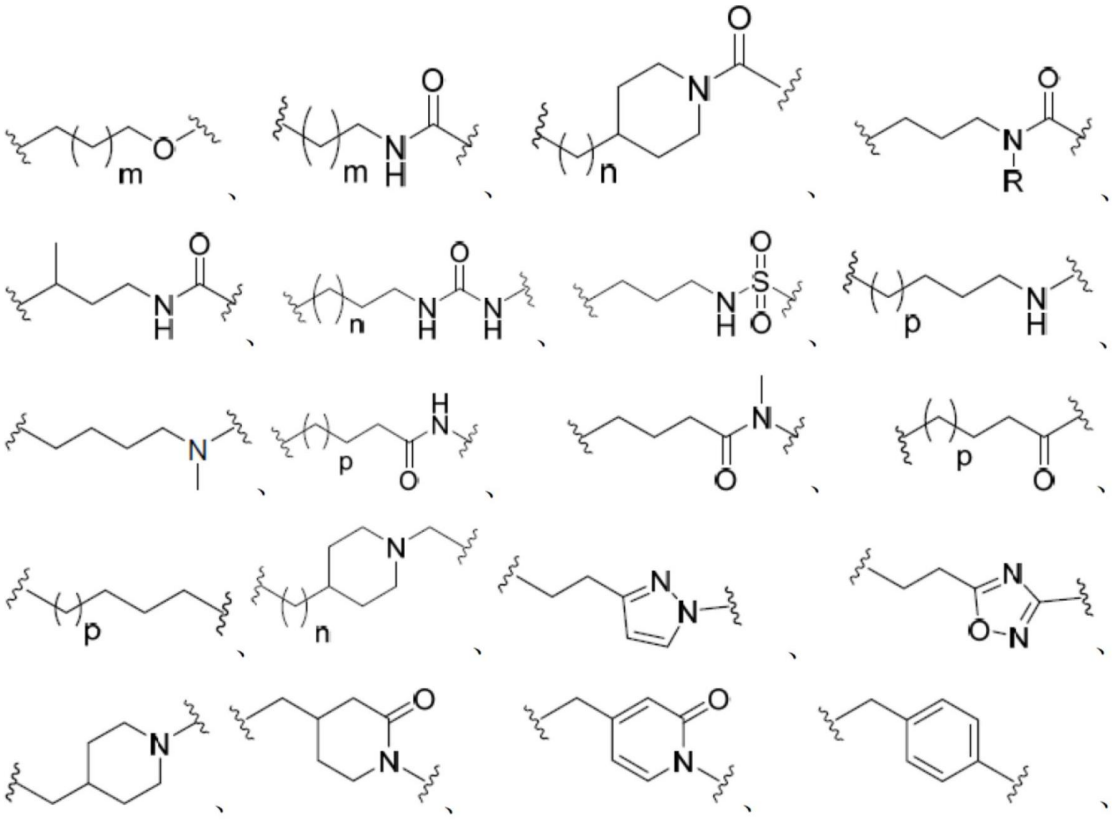
某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为CH_2OH。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为H。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为卤化物。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为碘、溴、氯或氟。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的至少一个实例为碘、溴、氯或氟，且R_1的其它实例为氢。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_1的所有实例为氢。

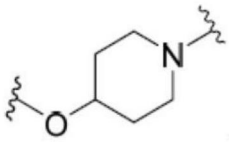
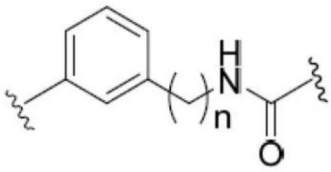
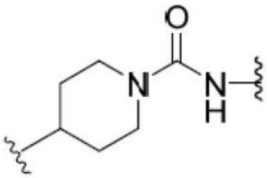
[0123] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R为H、烷基或芳基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R为H。在某些实施例中，本发明涉及上述化合物中的任一种，其中R为甲基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R为苯基。

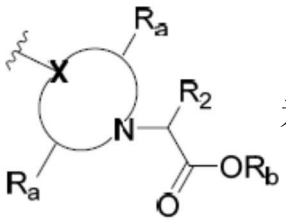
[0124] 在某些实施例中，本发明涉及上述化合物中的任一种，其中B为亚烷基、-亚烷基-(O)、-亚烷基-N(R)C(O)-、-亚烷基-(杂环基)-C(O)-、-亚烷基-C(O)N(R)-、-亚烷基-C(O)-、-亚烷基-N(R)-、-亚烷基-N(R)C(O)N(R)-、-亚烷基-N(R)SO_2-、-亚烷基-(芳基)-、-亚烷基-(杂环基)-、-亚烷基-(杂环基)-亚烷基-、-芳基-亚烷基-N(R)C(O)-、-芳基-C(O)N(R)-、-芳基-N(R)C(O)-、-(杂环基)-亚烷基-、-杂环基-亚烷基-N(R)C(O)-、-杂环基-C(O)N(R)-、-O-杂环基-、-亚烷基-O-、-杂环基-C(O)-、环亚烷基或环亚烷基-O-。

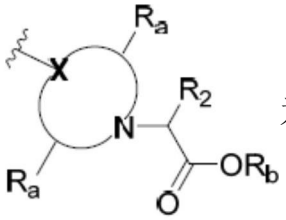
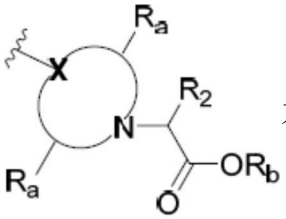
[0125] 在某些实施例中，本发明涉及上述化合物中的任一种，其中B选自由以下组成的群组：

[0126]



[0127]  、  和  ；m为0、1、2或3；n为0或1；且p为0、1或2。

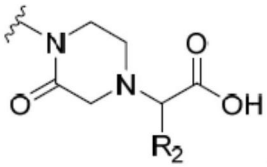
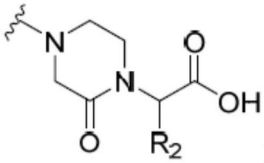
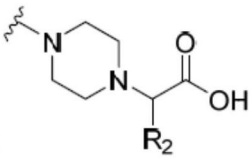
[0128] 在某些实施例中，本发明涉及上述化合物中的任一种，其中  为经R_1的一个或多个实例取代的3至12元杂环亚烷基。

[0129] 在某些实施例中，本发明涉及上述化合物中的任一种，其中  为未经取代的3至12元杂环亚烷基。在某些实施例中，本发明涉及上述化合物中的任一种，其中  为经R_1的一个或多个实例取代的3至12元杂环亚烷基，其中R_1为。

[0130] 在某些实施例中，本发明涉及上述化合物中的任一种，其中X为N。

[0131] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_a的两个实例为H。

[0132] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_b为H。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_b为(C1-C6)烷基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_b为甲基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_b为乙基。

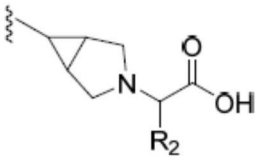
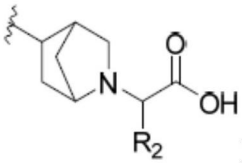
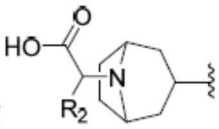
[0133] 在某些实施例中，本发明涉及上述化合物中的任一种，其中C选自由以下组成的群组：  、  和  。

[0134] 在某些实施例中，本发明涉及上述化合物中的任一种，其中X为$C(R_c)$。

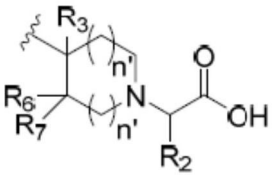
[0135] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_c为H、烷基、芳基、OH或卤化物。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_c为H。

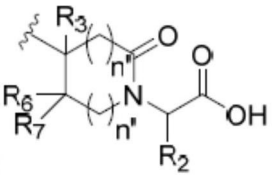
[0136] 在某些实施例中，本发明涉及上述化合物中的任一种，其中两个R_a的实例一起形成键，或(C1-C4)-亚烷基桥。

[0137] 在某些实施例中，本发明涉及上述化合物中的任一种，其中C为

 、  或  。

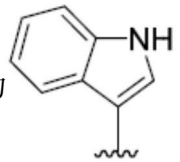
[0138] 在某些实施例中，本发明涉及上述化合物中的任一种，其中C表示

 。在某些实施例中，本发明涉及上述化合物中的任一种，其中C表示

 。

[0139] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为H、烷基、经取代或未经取代的芳基、经取代或未经取代的杂芳基、环烷基、-亚烷基-烷氧基、亚烷基-芳基或杂环烷基。

[0140] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为H、(C_1-C_4)烷基、环丙基、CH_2OMe、苯基、-CH_2Ph、吡啶基或吲哚基。

[0141] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为H。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为Me。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为未经取代的苯基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为经取代的苯基。在某些实施例中，本发明涉及上述化合物中的任一种，其中所述经取代的苯基经烷氧基、卤化物、-C(O)NH_2或-C(O)烷基的一个或多个独立实例取代。在某些实施例中，本发明涉及上述化合物中的任一种，其中所述经取代的苯基经至少一个卤化物取代。在某些实施例中，本发明涉及上述化合物中的任一种，其中所述卤化物为Cl。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为未经取代的吡啶基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为经取代的吡啶基。在某些实施例中，本发明涉及上述化合物中的任一种，其中所述经取代的吡啶基经NH_2或OH取代。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_2为  。

[0142] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_3为H、卤化物、CF_3、烷基、亚烷基-烷氧基、芳基、羟基或烷氧基。

[0143] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_3为H、卤化物、Me、OMe或Ph。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_3为碘、溴、氯或氟。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_3为H。

[0144] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_6为H、卤化物、CF_3、烷

基、亚烷基-烷氧基、芳基、羟基或烷氧基。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_6为H。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_6为OMe。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_6为Me。

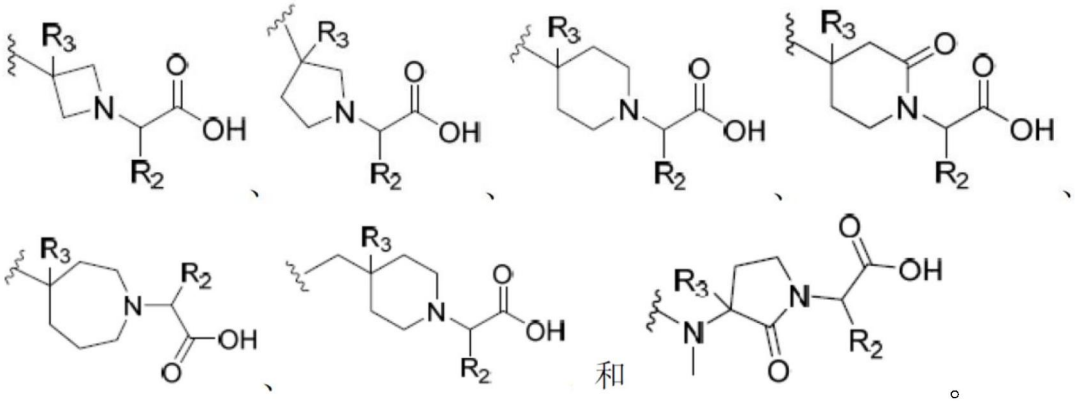
[0145] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_7为H、卤化物、CF_3、烷基、亚烷基-烷氧基、芳基、羟基或烷氧基。

[0146] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_7为H。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_7为OMe。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_7为Me。在某些实施例中，本发明涉及上述化合物中的任一种，其中R_7为CH_2OH。

[0147] 在某些实施例中，本发明涉及上述化合物中的任一种，其中R_3为H或F，R_6为H，且R_7为H或CH_2OH。

[0148] 在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的仅一个实例为0。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的至少一个实例为0。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的两个实例均为0。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的仅一个实例为1。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的至少一个实例为1。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的两个实例均为1。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的仅一个实例为2。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的至少一个实例为2。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的两个实例均为2。在某些实施例中，本发明涉及上述化合物中的任一种，其中n'的一个实例为0，且n'的一个实例为1。

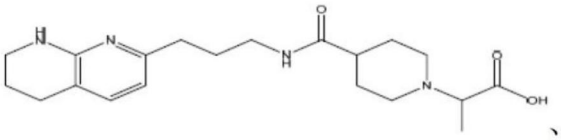
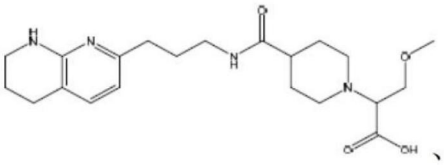
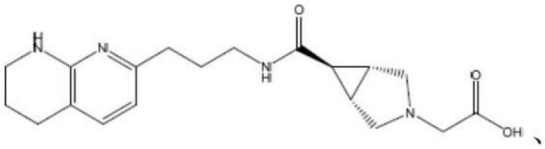
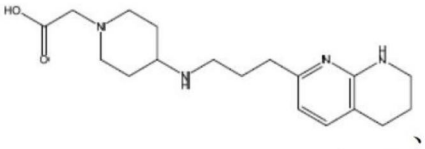
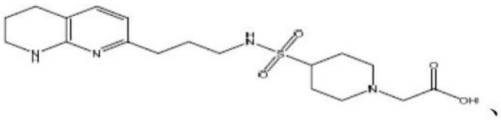
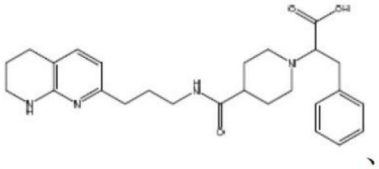
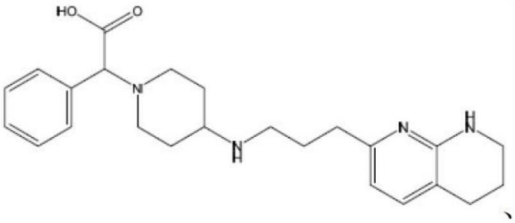
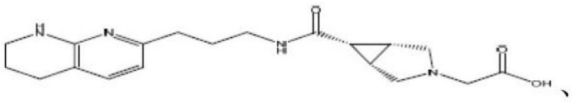
[0149] 在某些实施例中，本发明涉及上述化合物中的任一种，其中C选自由以下组成的群组：

[0150] 

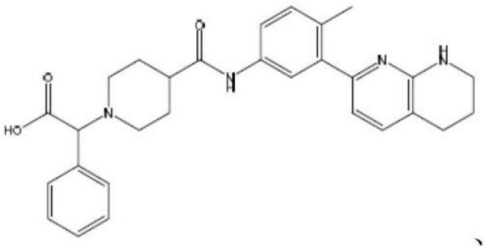
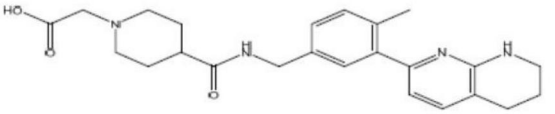
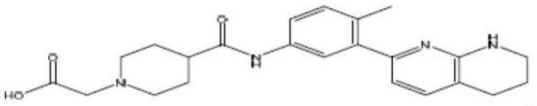
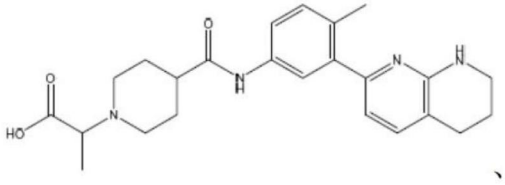
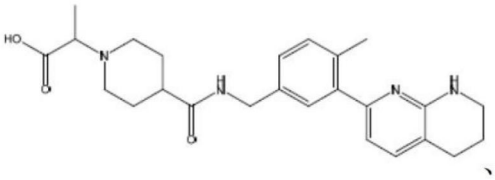
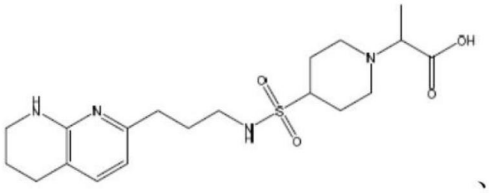
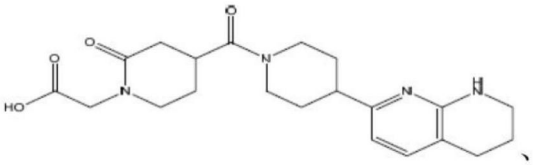
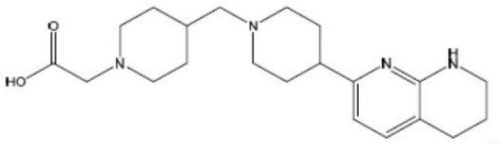
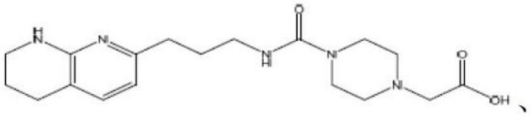
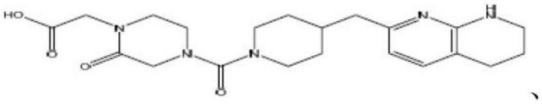
[0151] 在某些实施例中，本发明涉及上述化合物中的任一种，其中可选取代基(当存在时)选自由以下组成的群组：烷氧基、烷基酯、烷基羰基、羟烷基、氰基、卤、氨基、酰胺基、环烷基、芳基、卤烷基、硝基、羟基、烷氧基、芳氧基、烷基、烷硫基和氰基烷基。

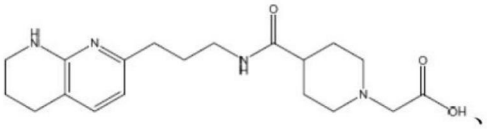
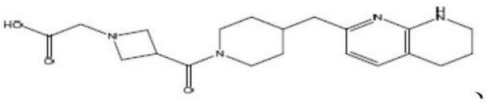
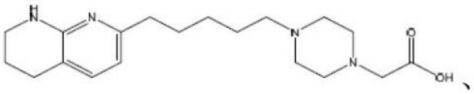
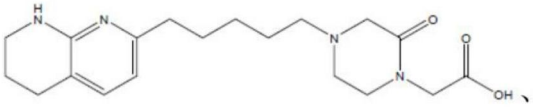
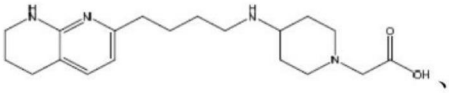
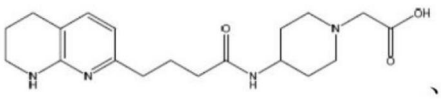
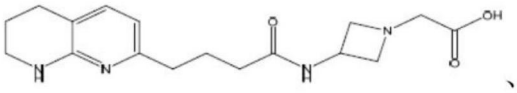
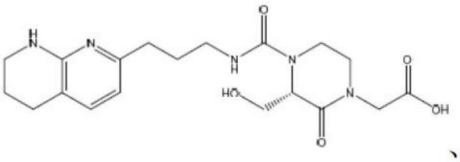
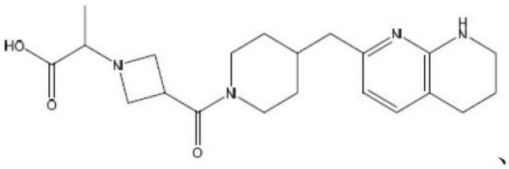
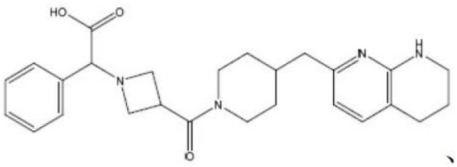
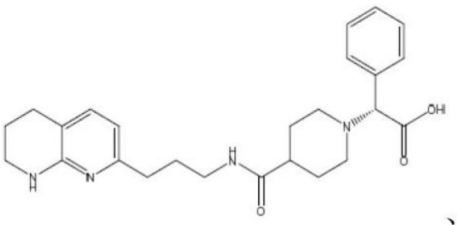
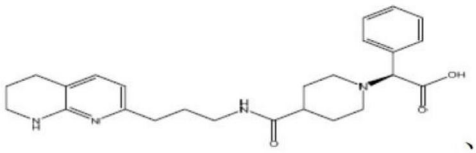
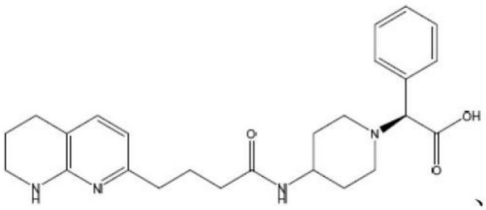
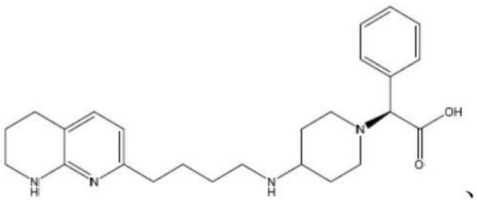
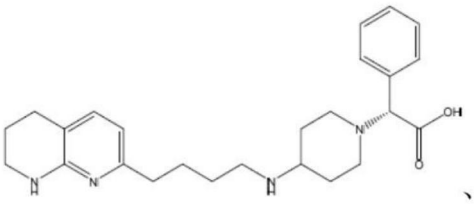
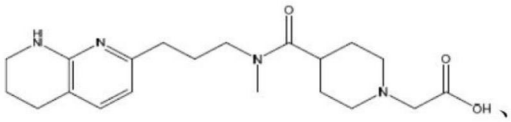
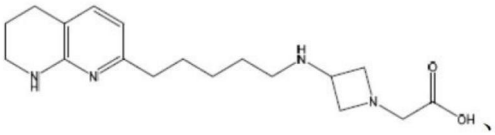
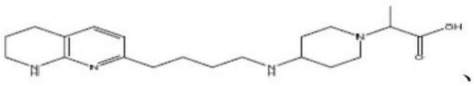
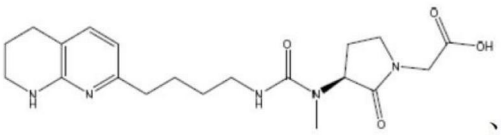
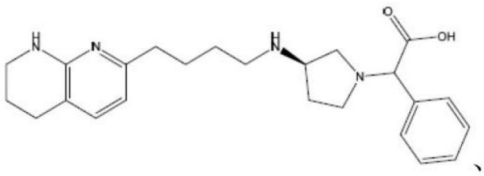
[0152] 在某些实施例中，本发明涉及上述化合物中的任一种，其中所述化合物为药学上可接受的盐。

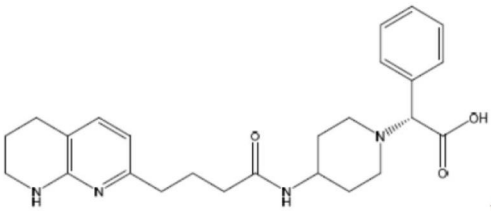
[0153] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

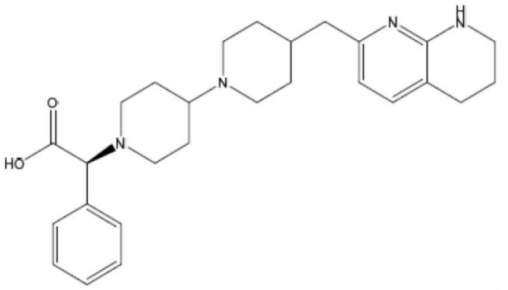









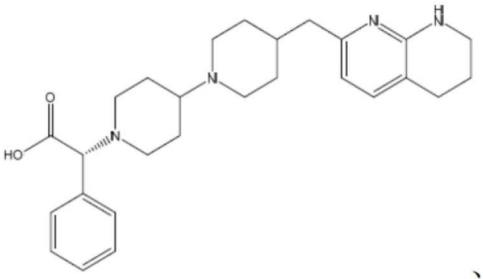
[0154]

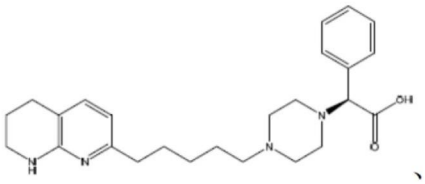











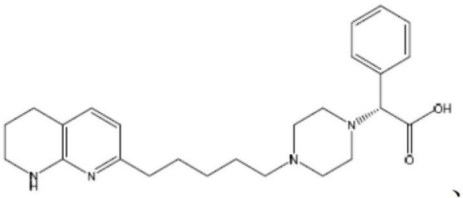










[0155]











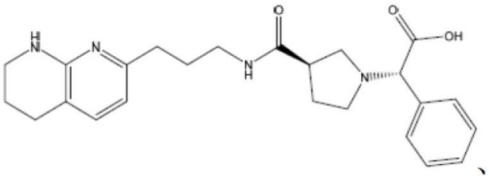




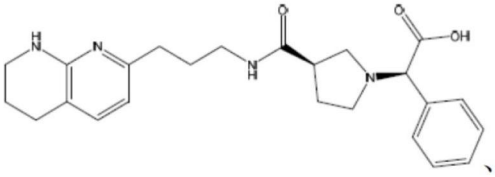


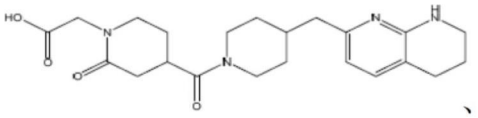


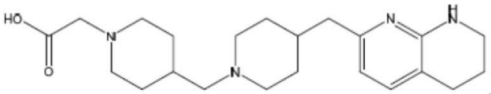


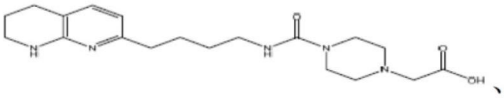


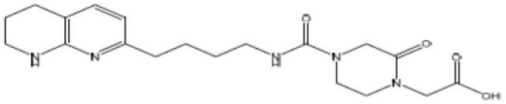
[0156]

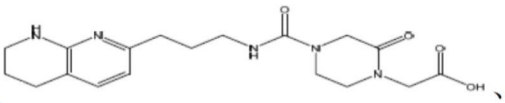


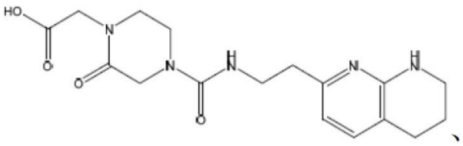


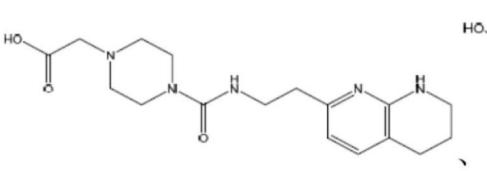


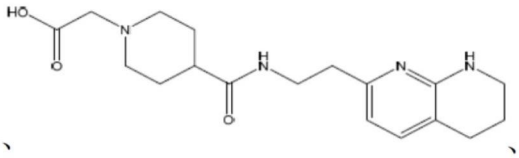


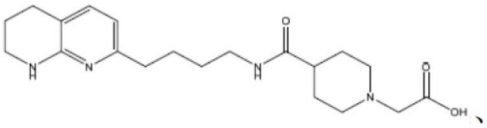


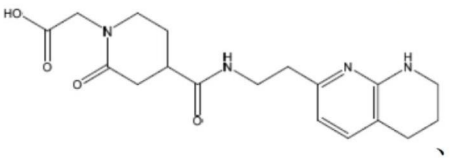


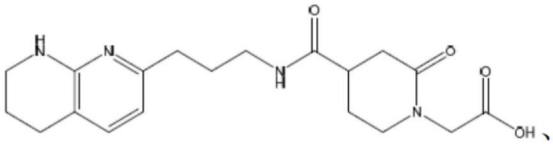
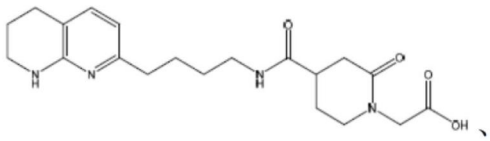
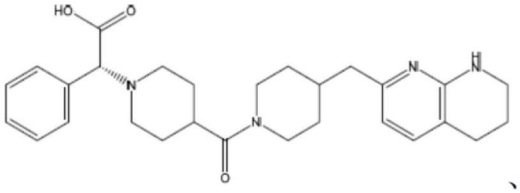
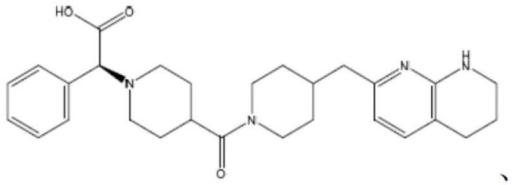
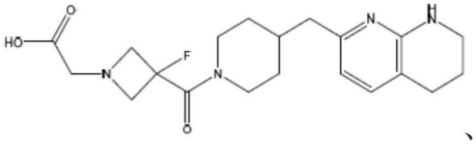
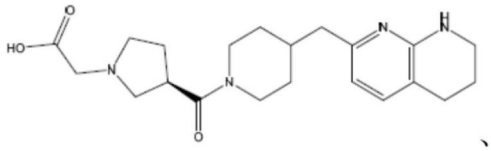
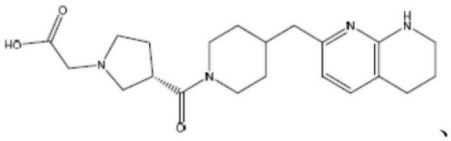
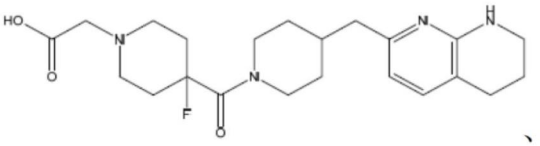




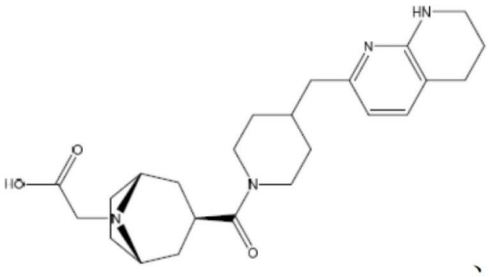
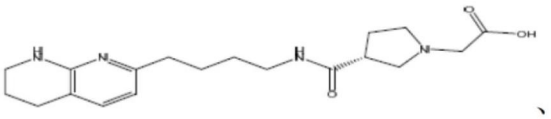
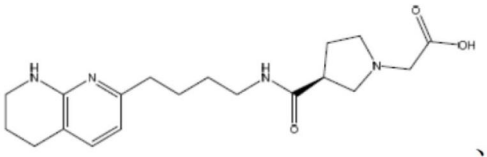
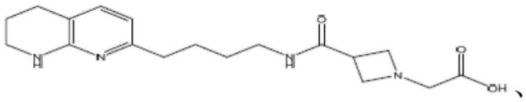
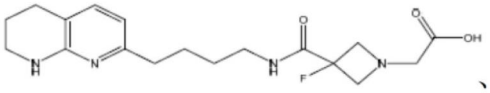
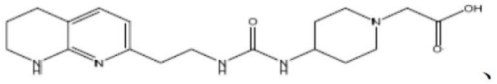
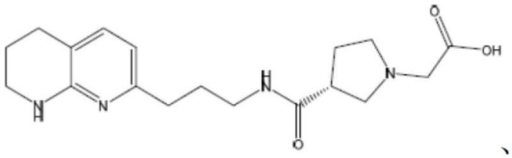
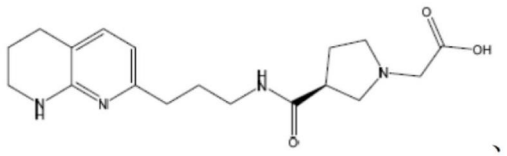
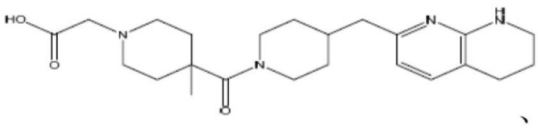
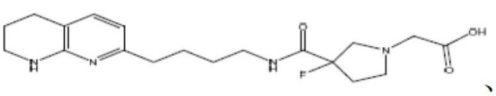
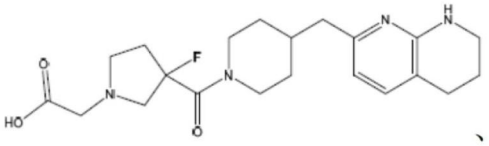
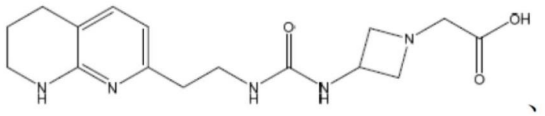


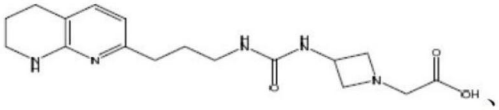


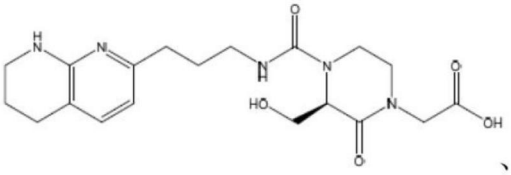


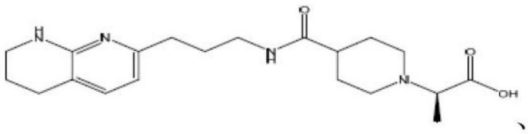









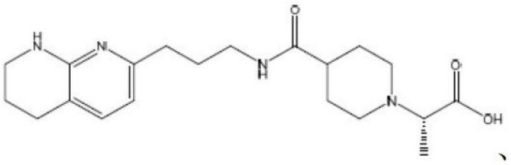
[0157]

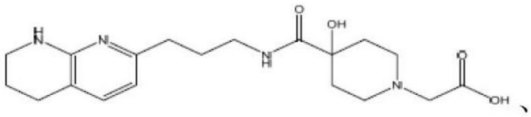













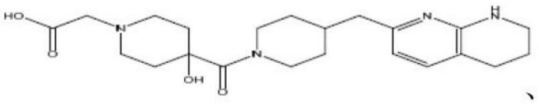


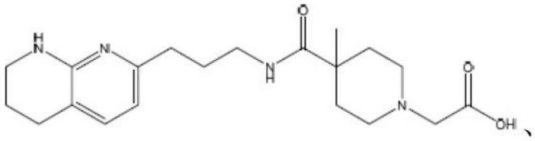


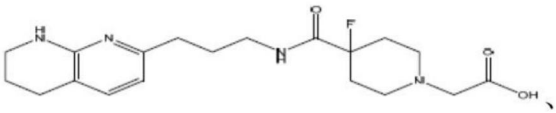


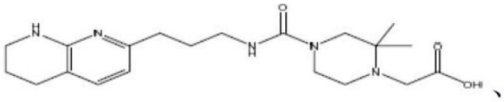


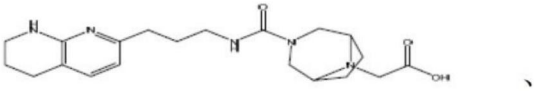




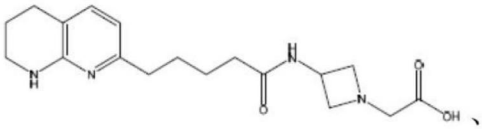


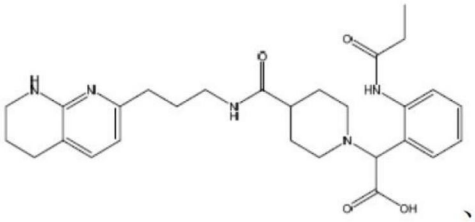


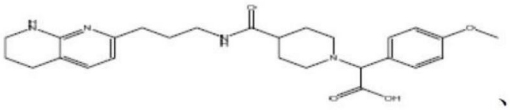


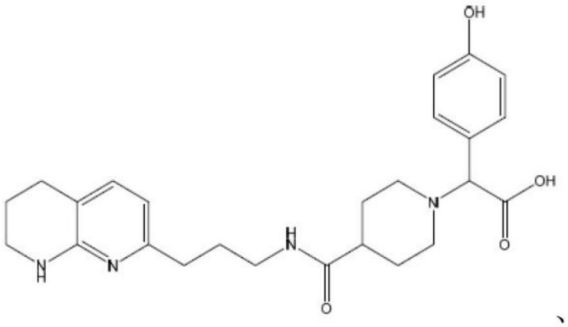


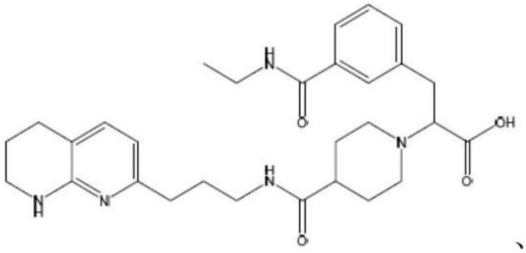
[0158]

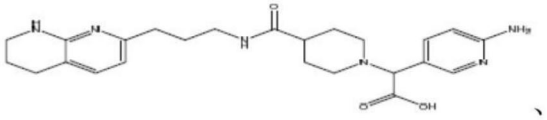


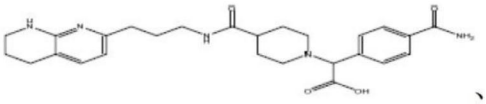


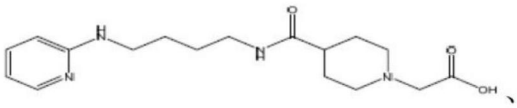


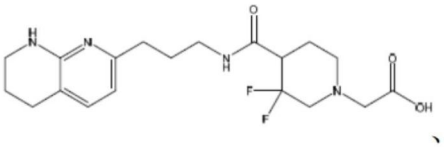


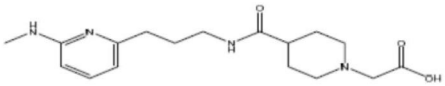


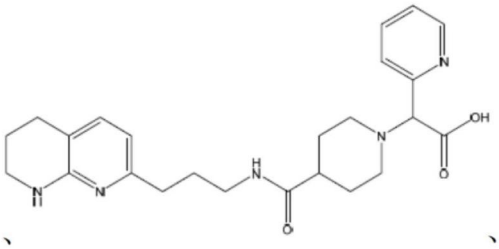


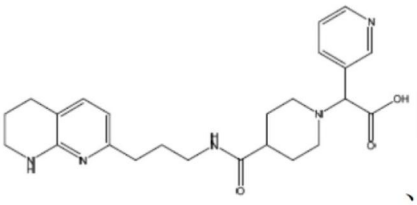


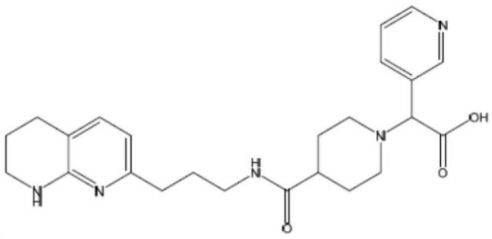




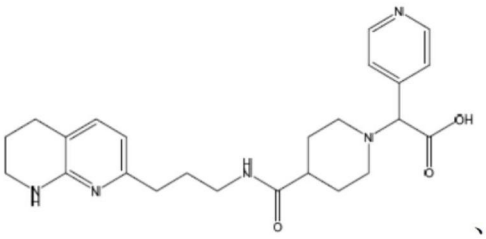


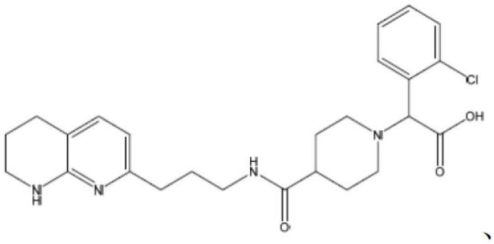


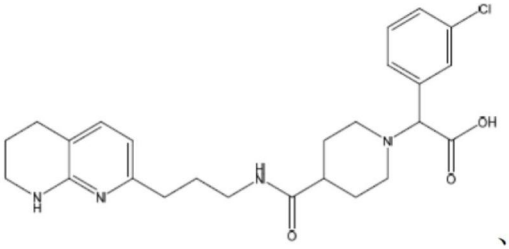


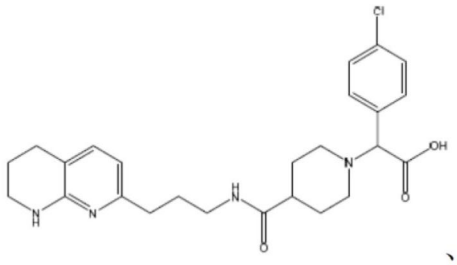


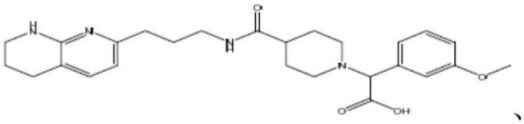
[0159]

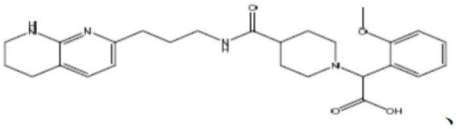


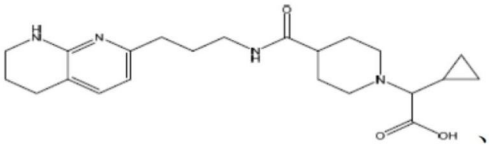


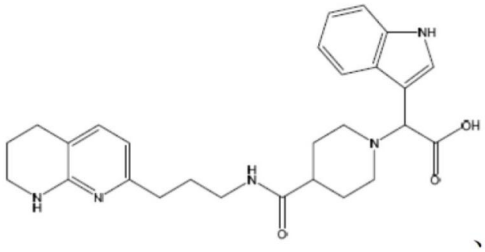


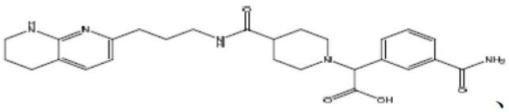


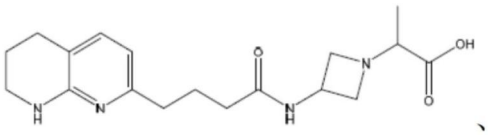


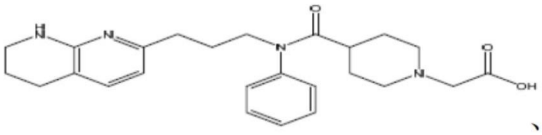
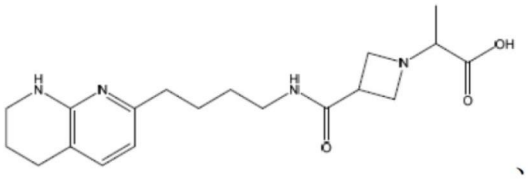
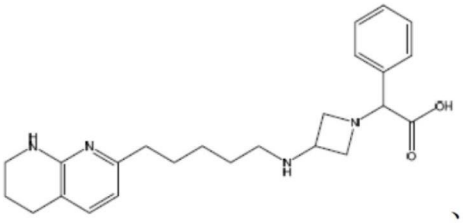
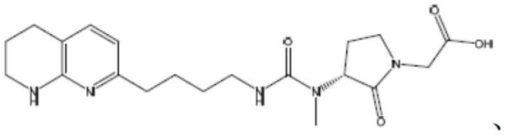
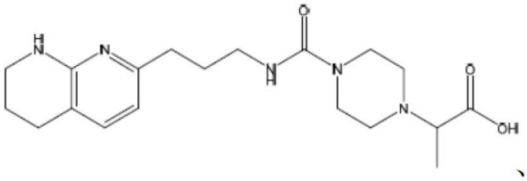
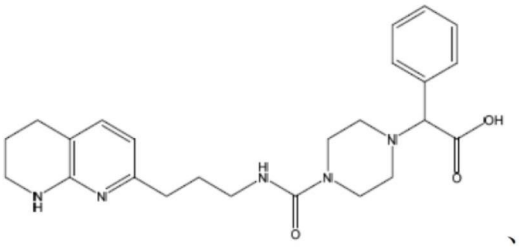




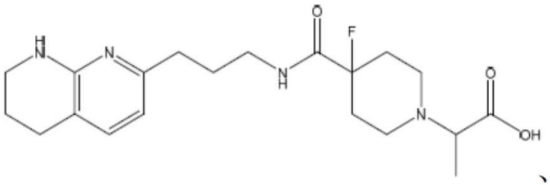
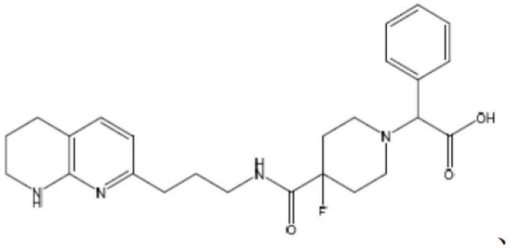
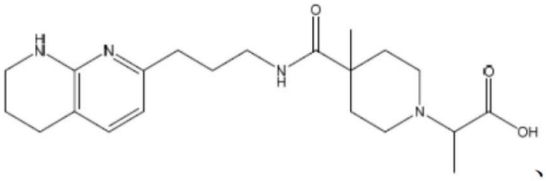
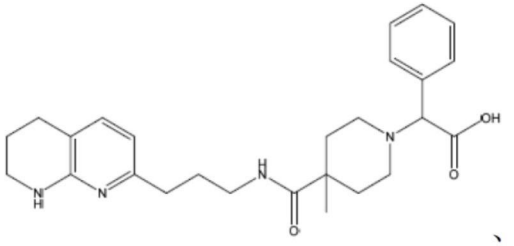
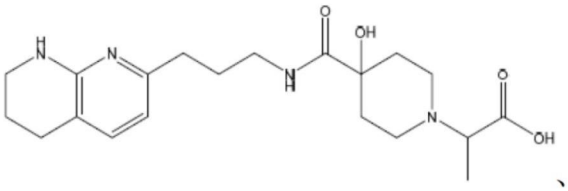
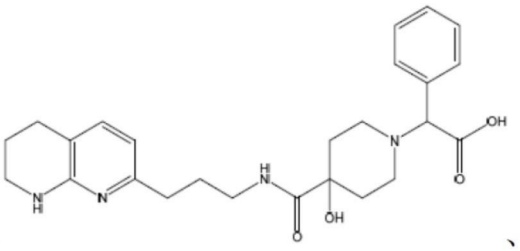
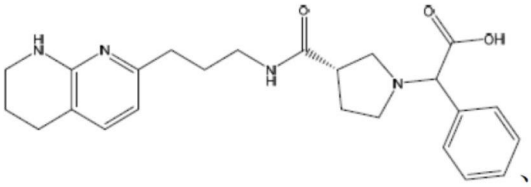
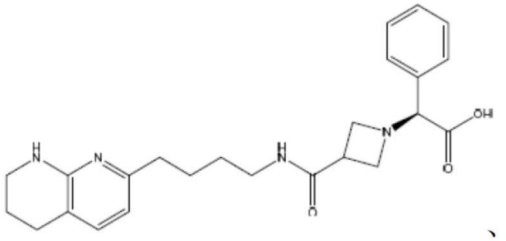


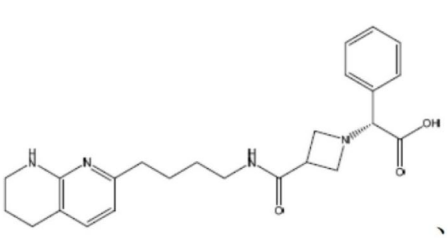


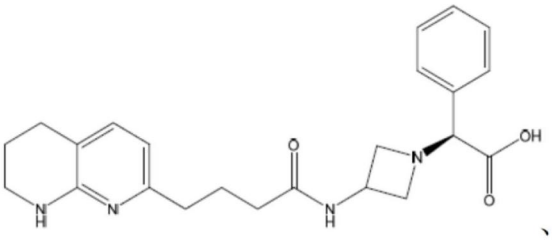


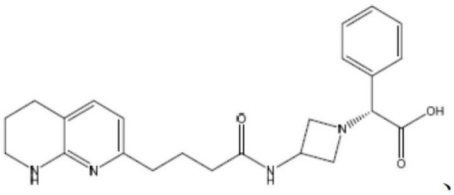







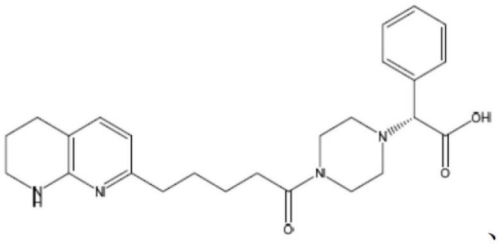
[0160]

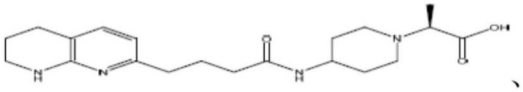









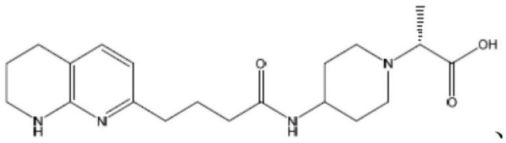




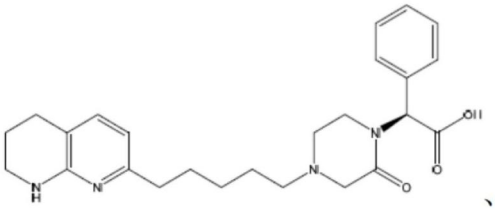


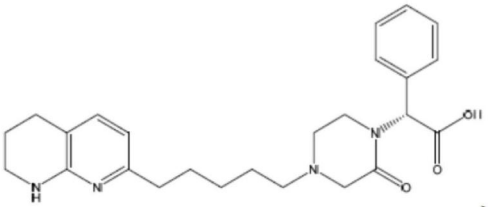


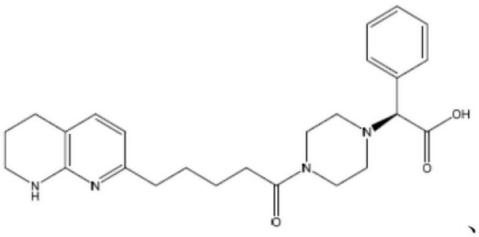


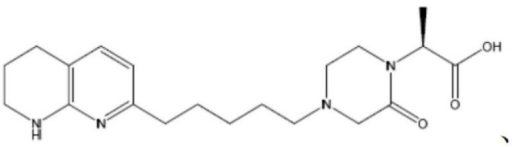


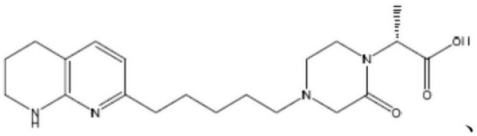
[0161]

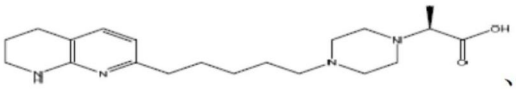


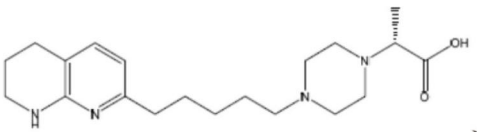


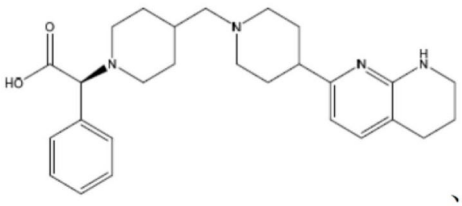


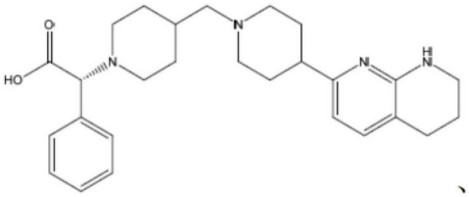


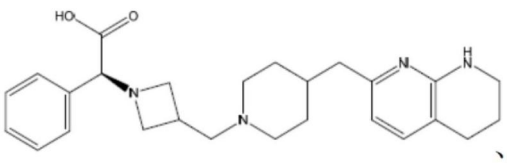


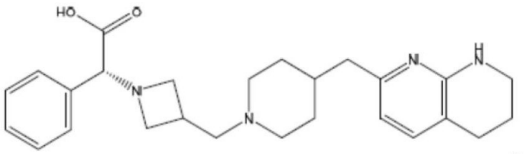
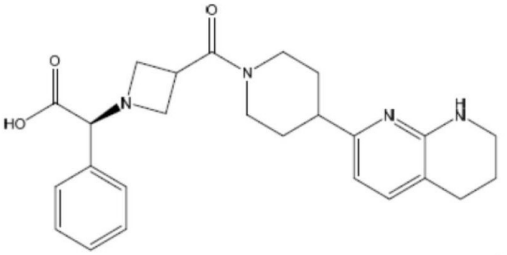


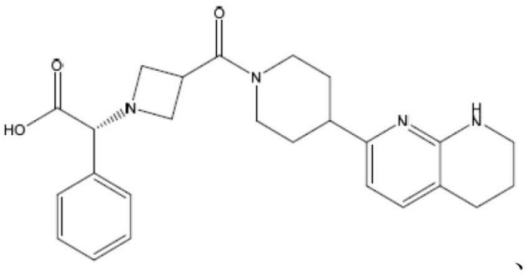
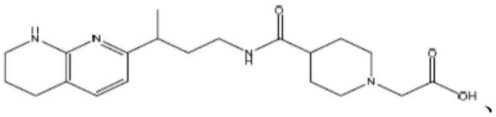


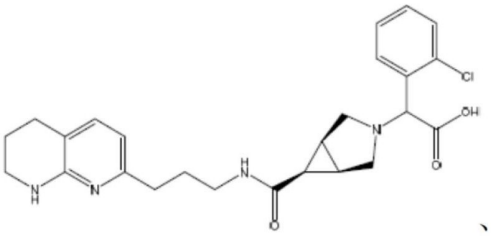


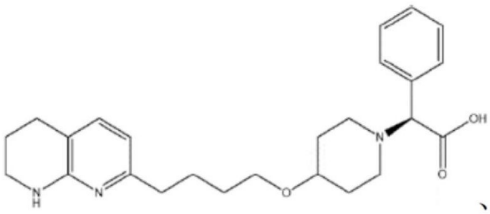
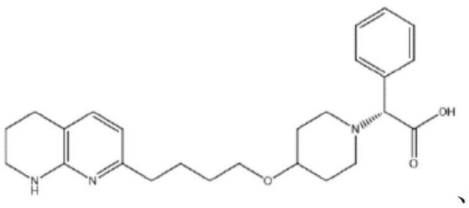


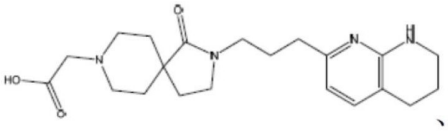
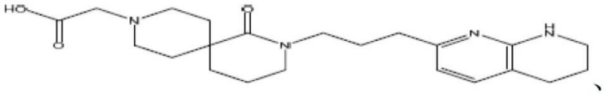


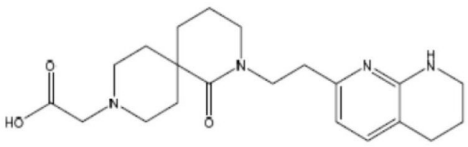
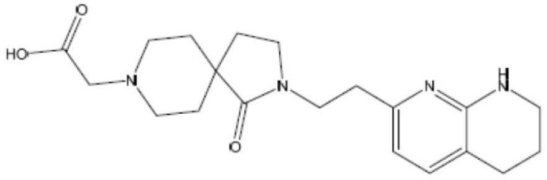
 、  、

 、  、

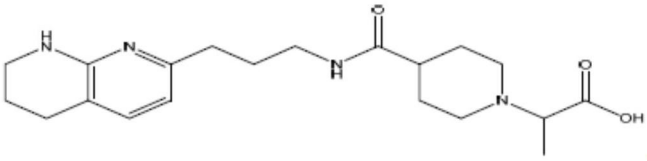
[0162]  、

 、  、

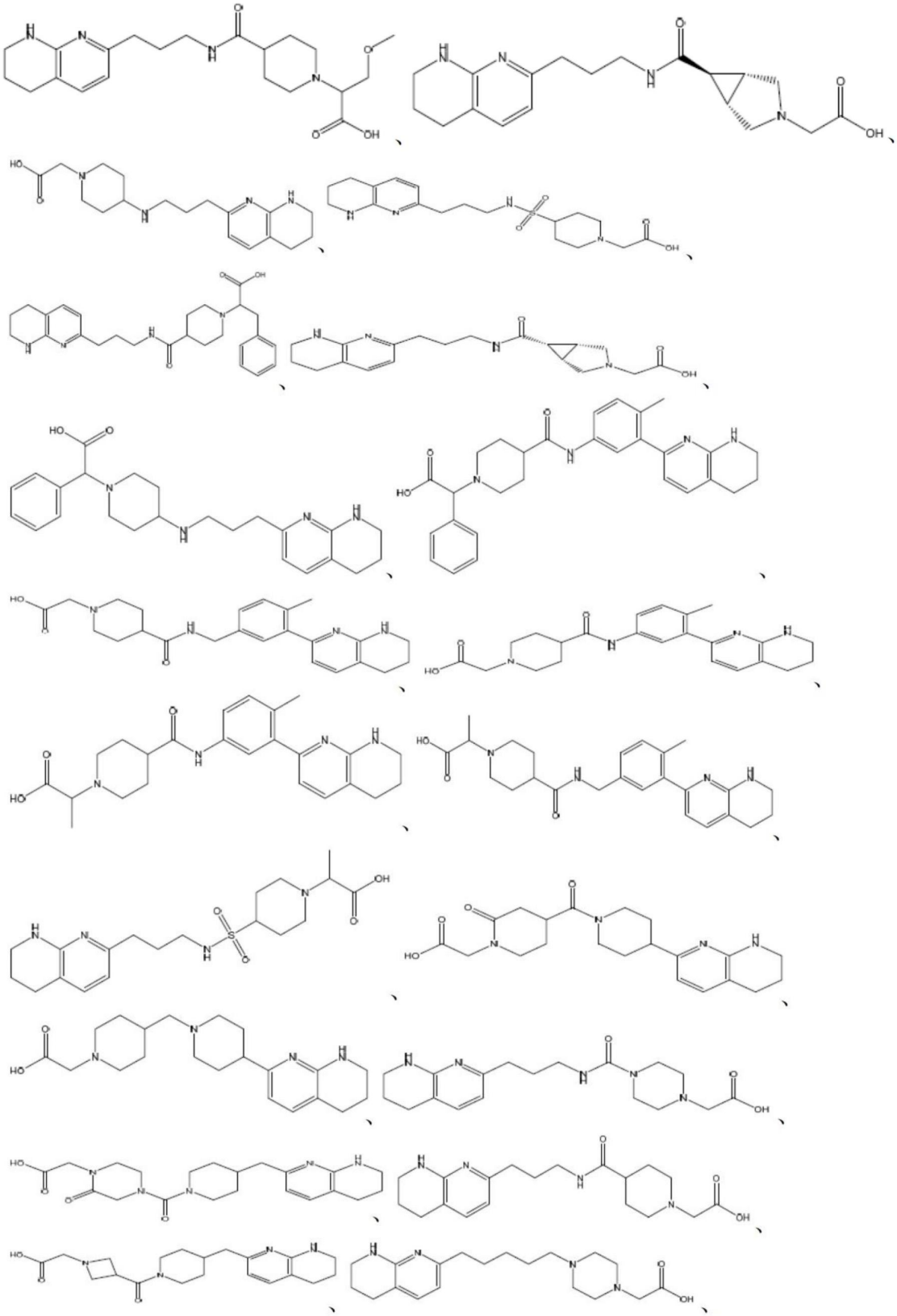
 、  、

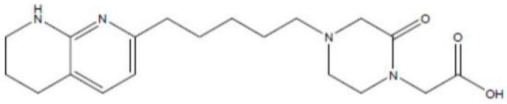
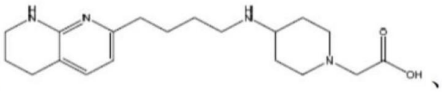
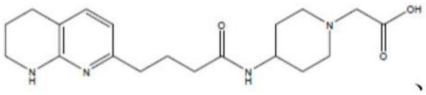
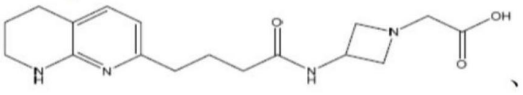
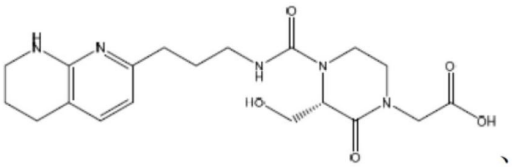
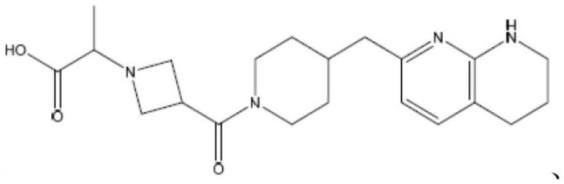
 和  。

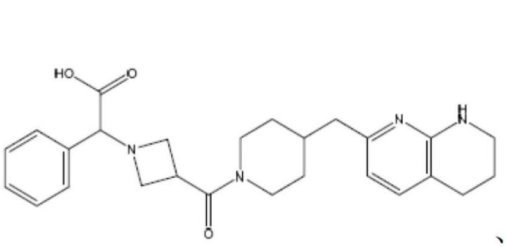
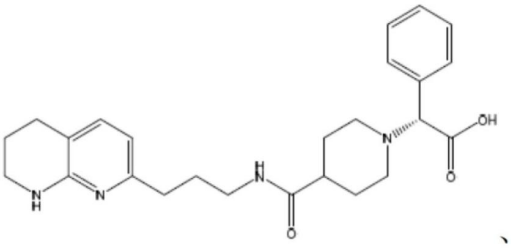
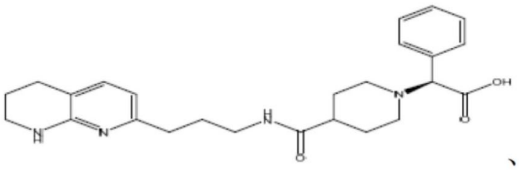
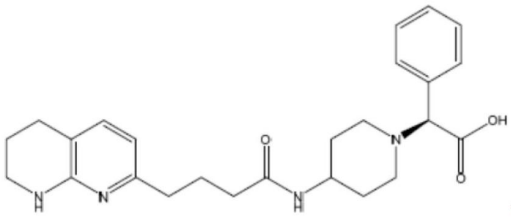
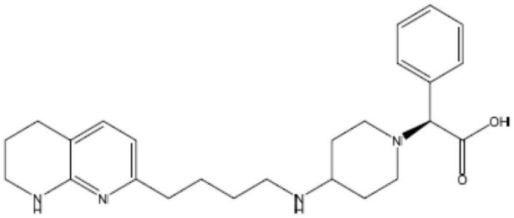
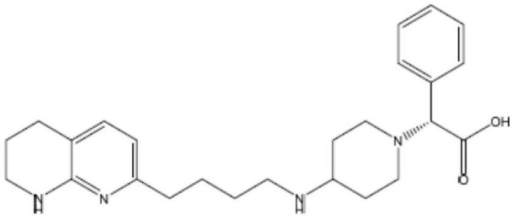
[0163] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

[0164]  、

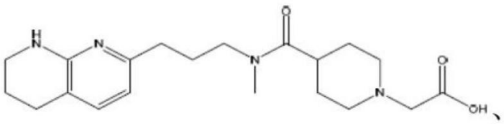
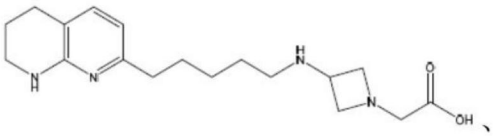
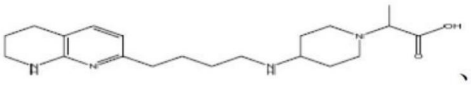
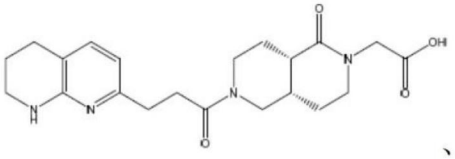
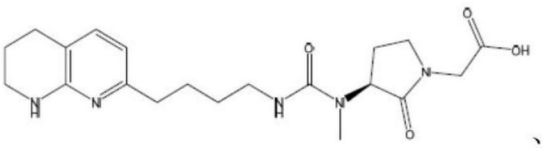
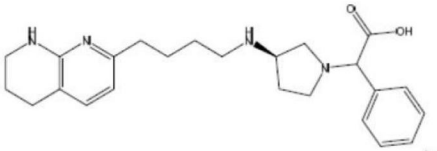
[0165]

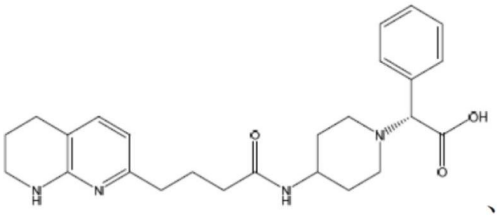


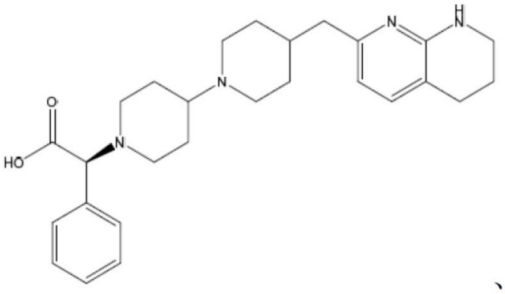

、

、

、

、

、

、

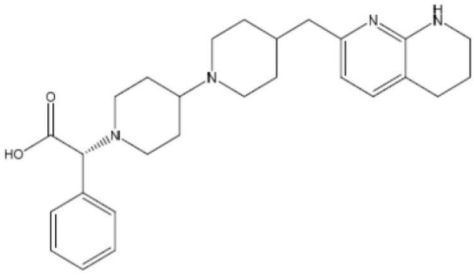
[0166]

、

、

、

、

和

。

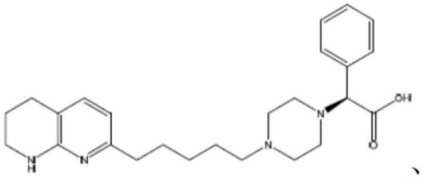
[0167] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

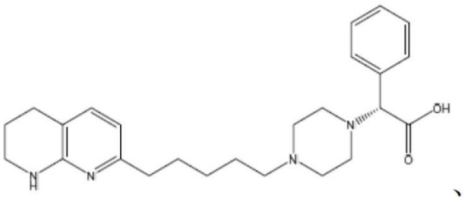
[0168]

、

、

、

、

、

、

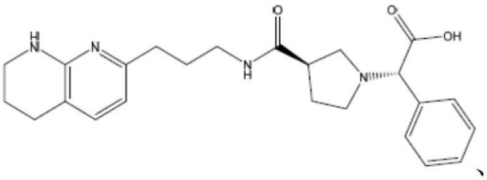




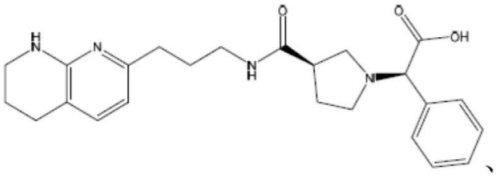


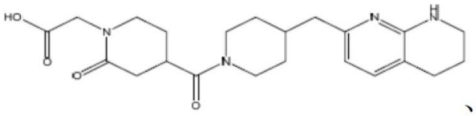


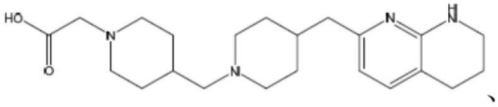


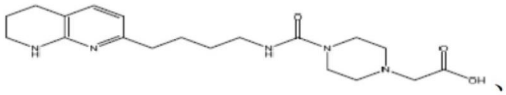


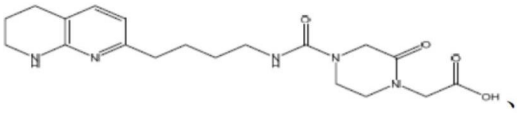
[0169]

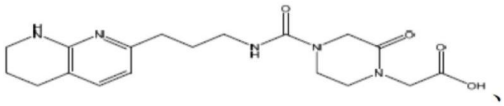


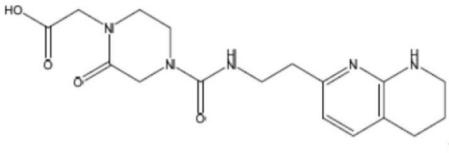


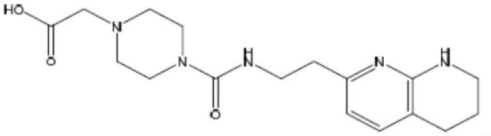


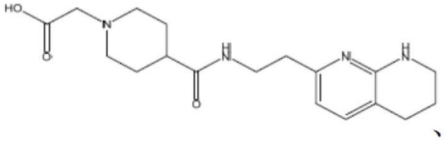


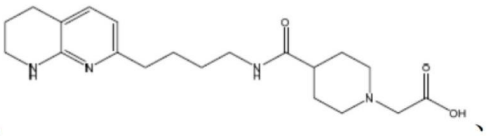


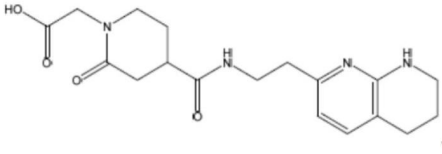


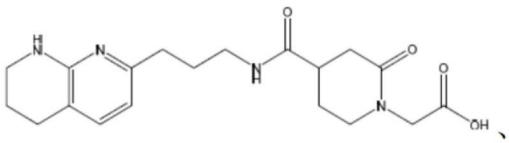


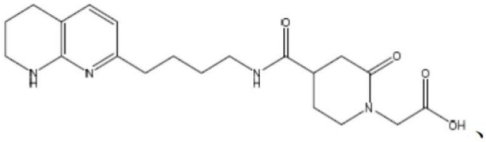
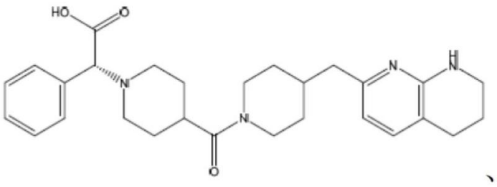
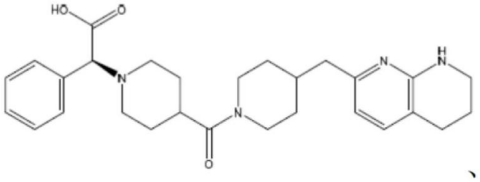
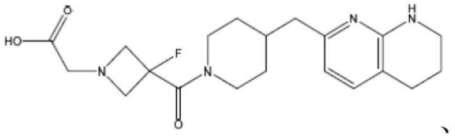
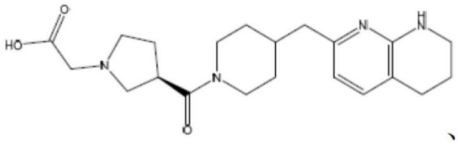
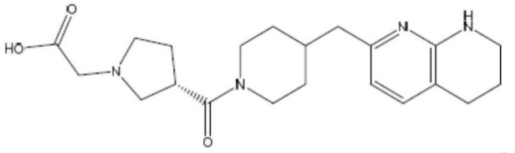


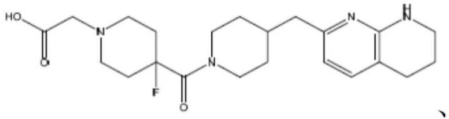
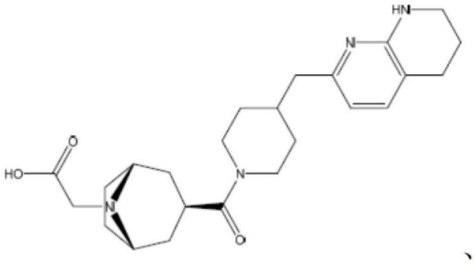
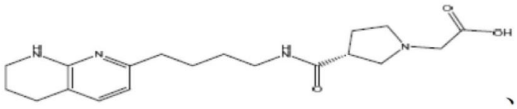
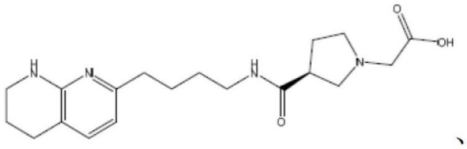
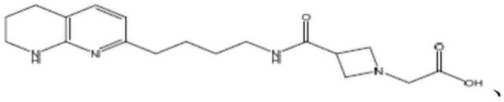
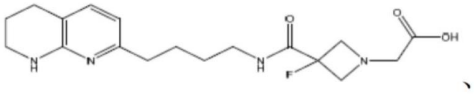
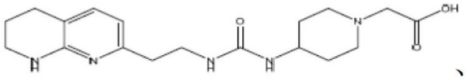
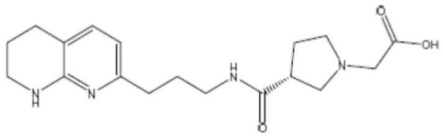
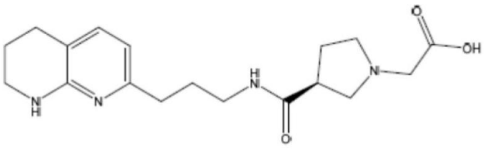






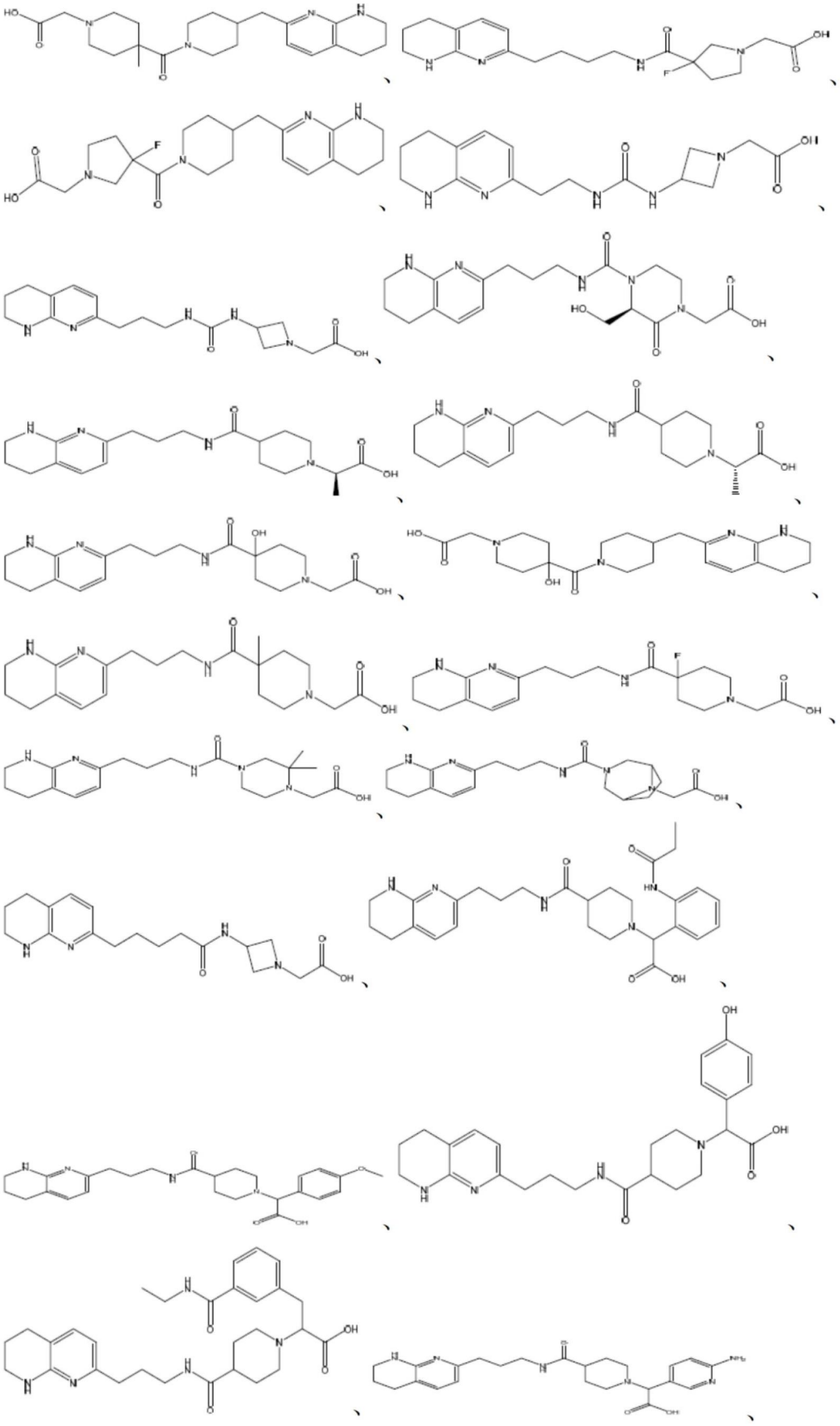


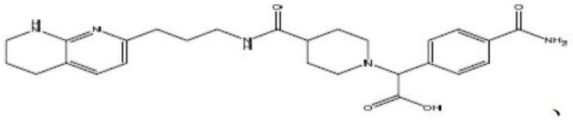
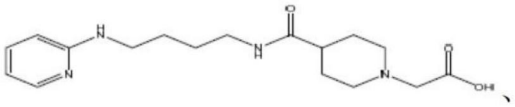
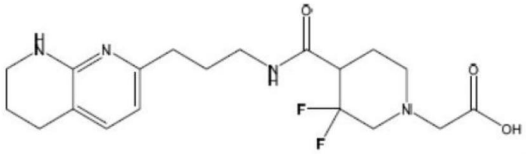
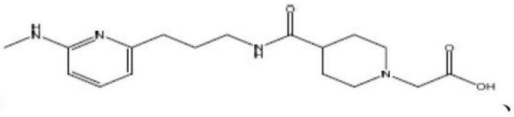
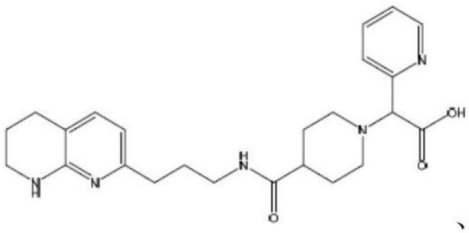
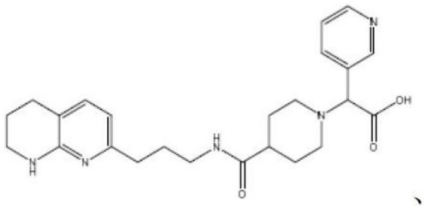
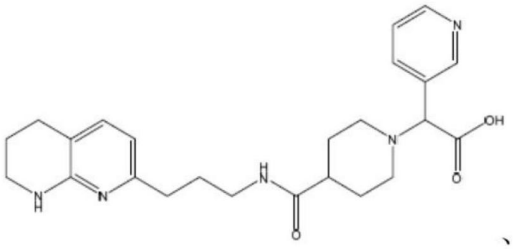
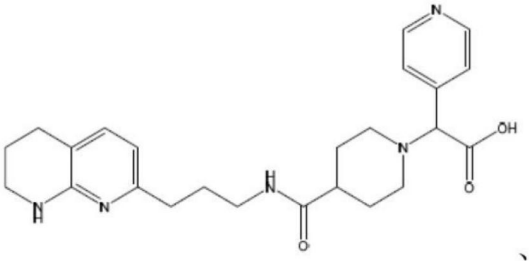
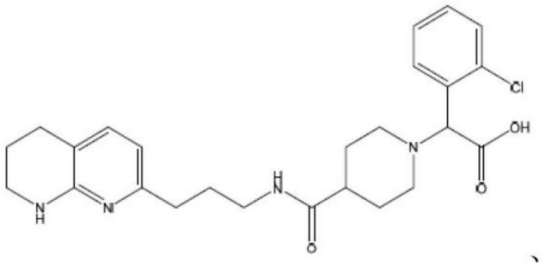
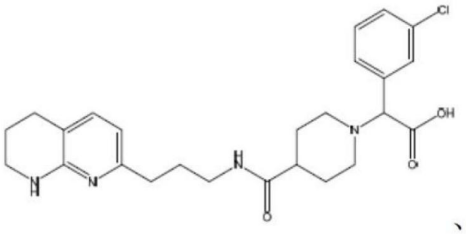
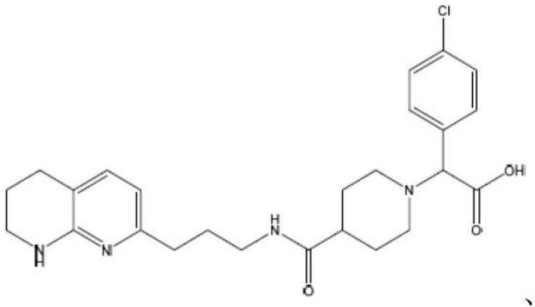
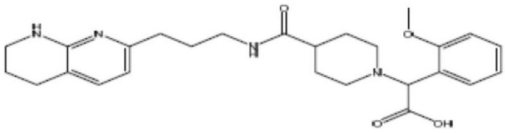

、

、

、

、

、

、

[0170]

、

、

、

、

、

、

、

和

。

[0171] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

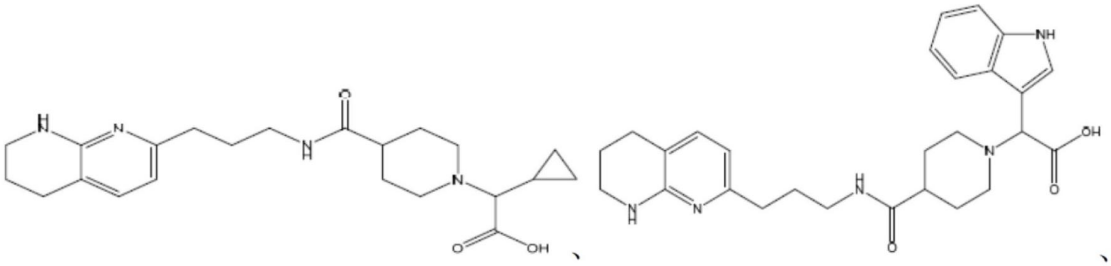
[0172]

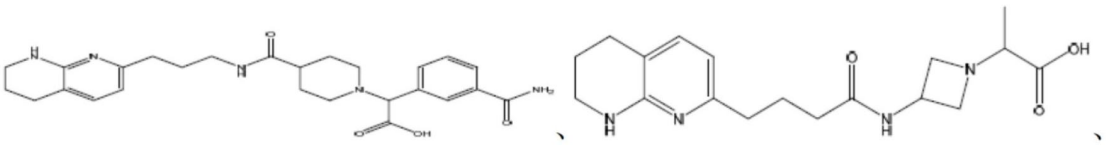


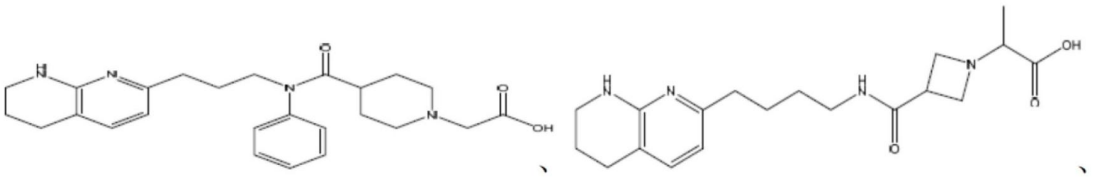
[0173]  、  、  、  、  、  、  、  、  、  、  、、 

和 。

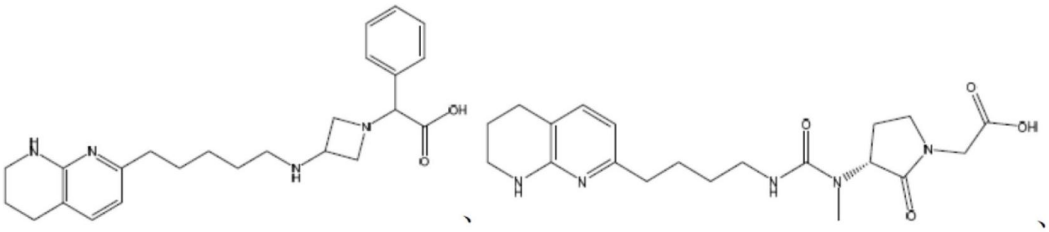
[0174] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

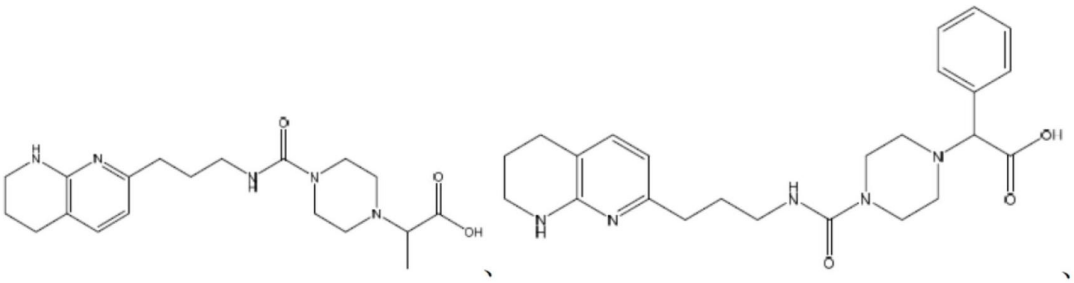


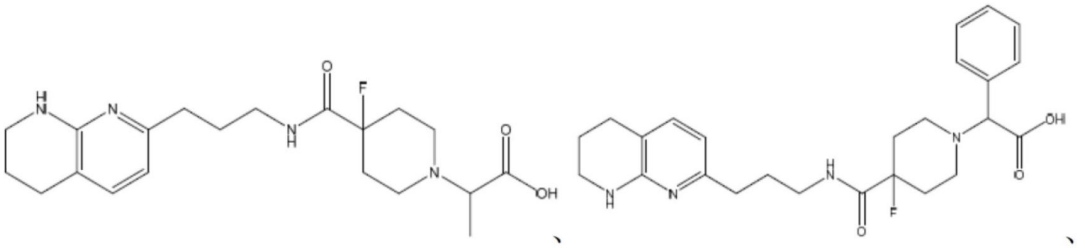


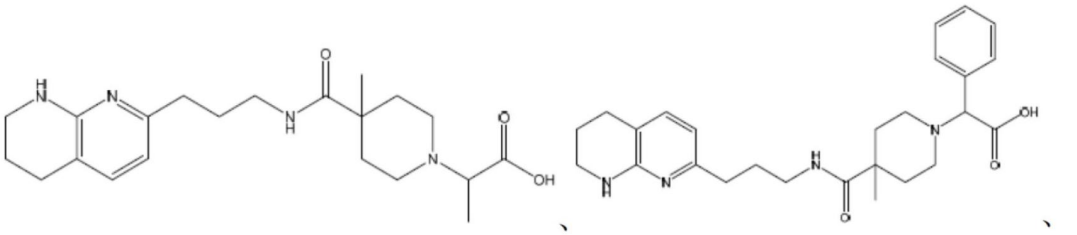


[0175]

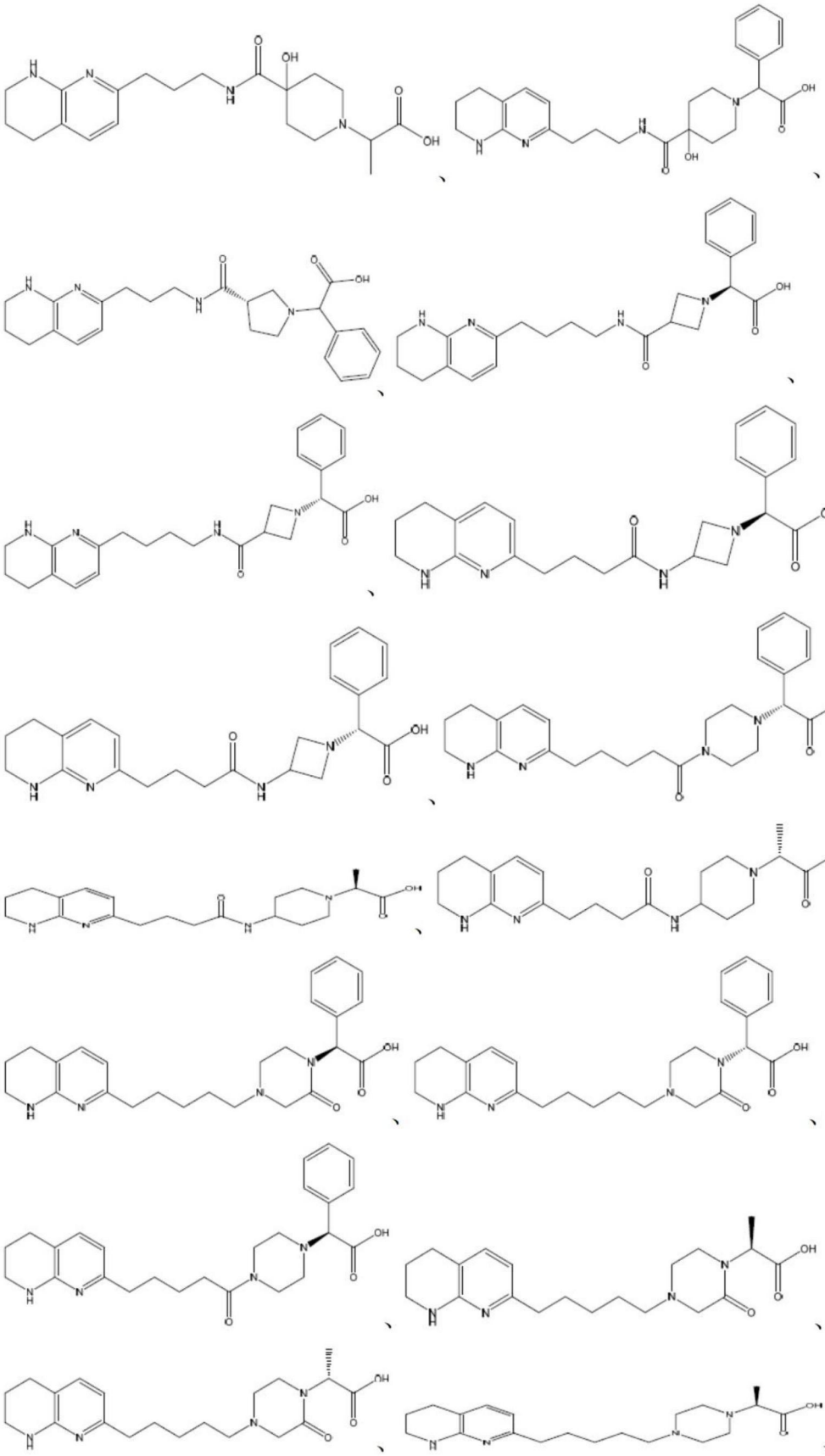


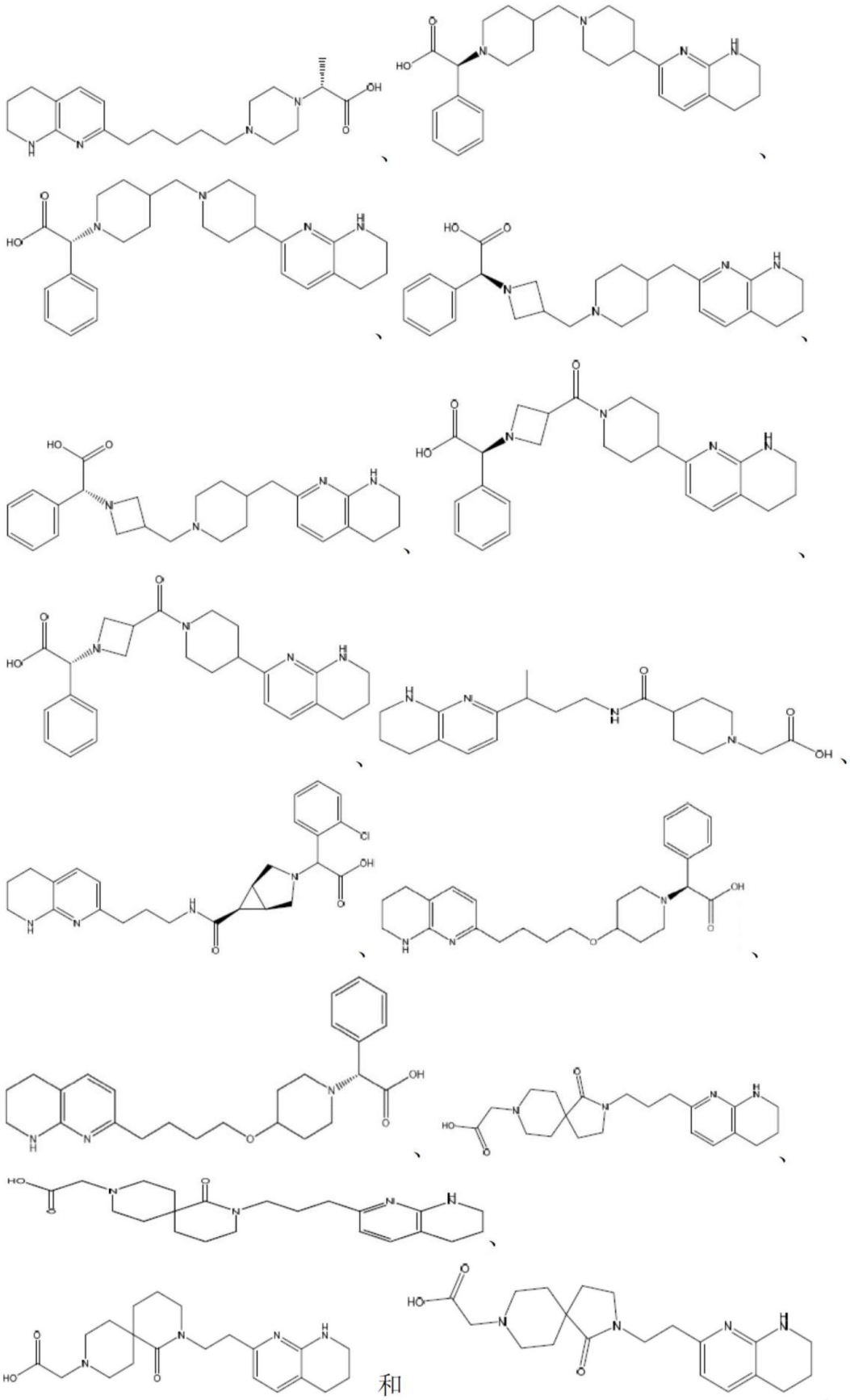




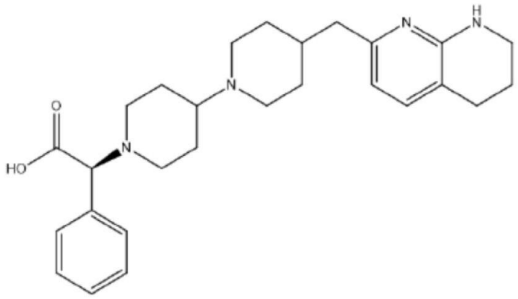
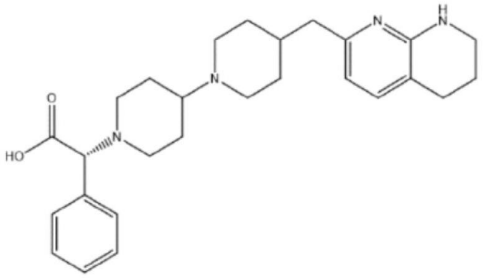
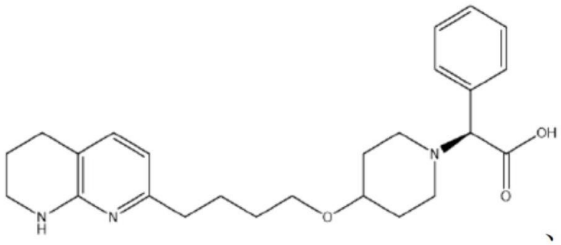
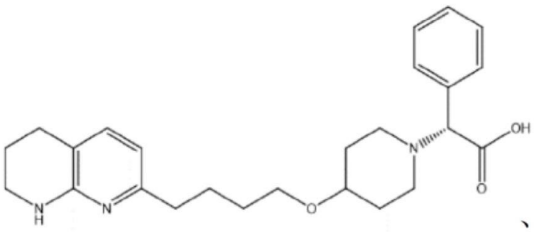


[0176]

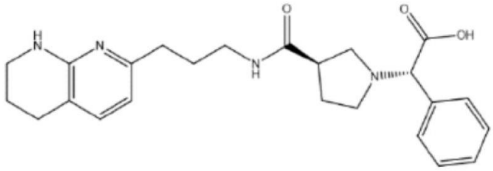
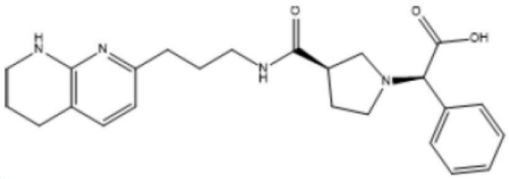
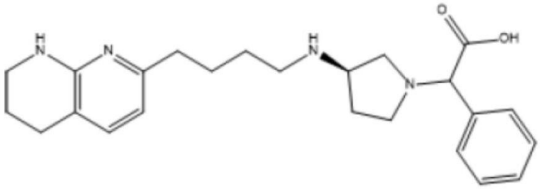
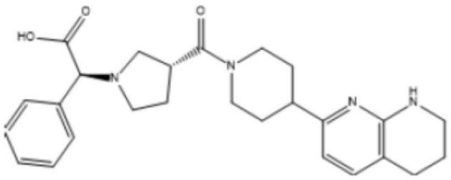
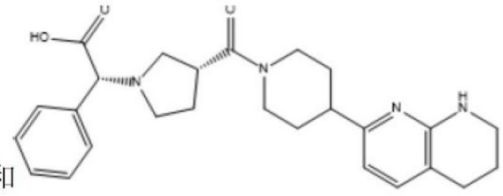


[0177] 

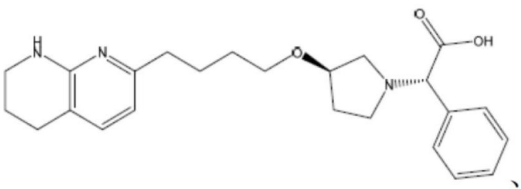
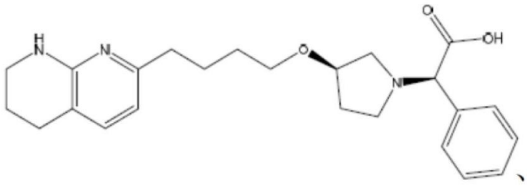
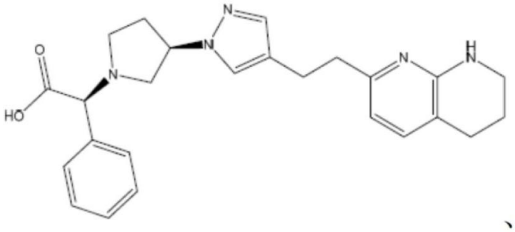
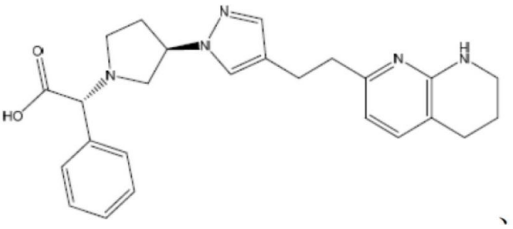
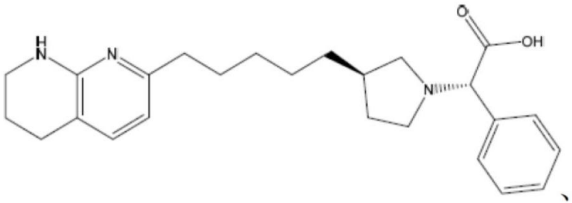
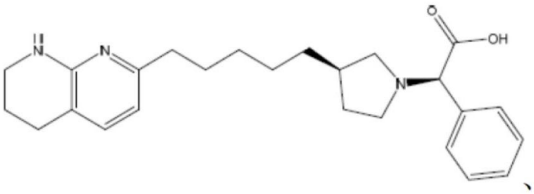
[0178] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：


、

、

、

、

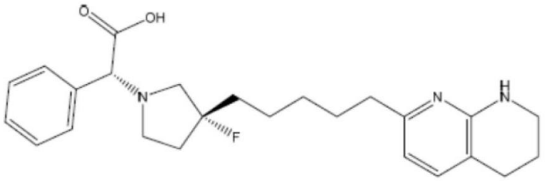
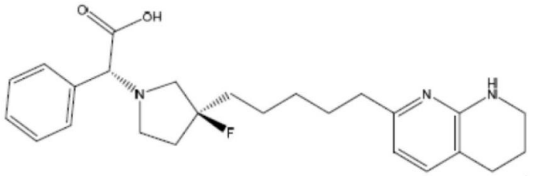
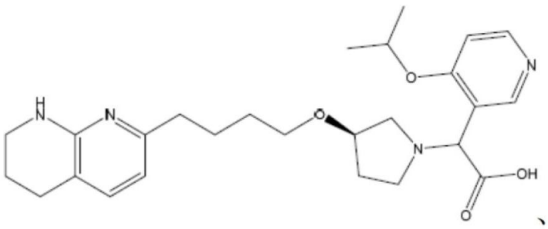
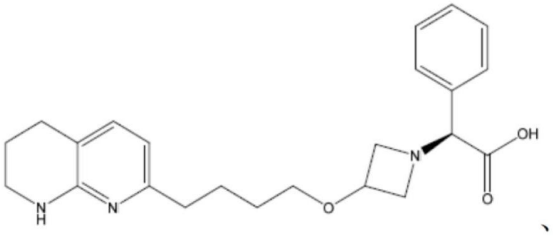
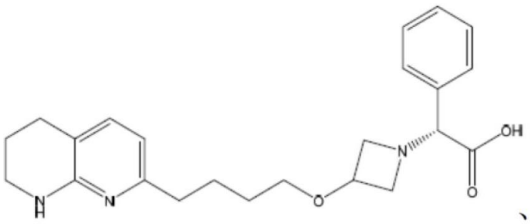
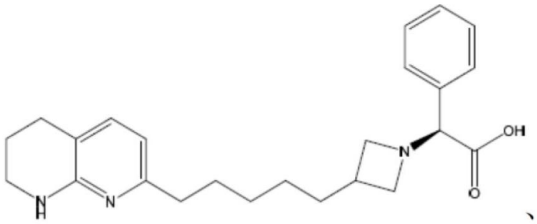
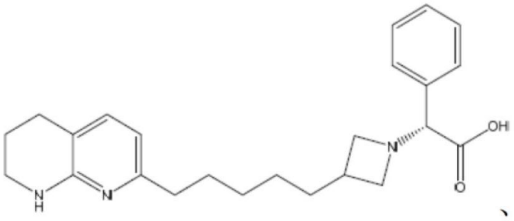
[0179]

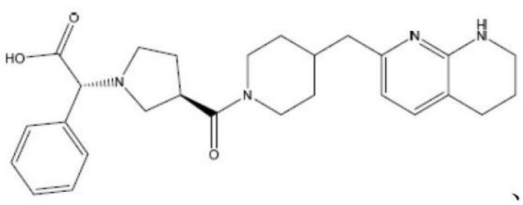
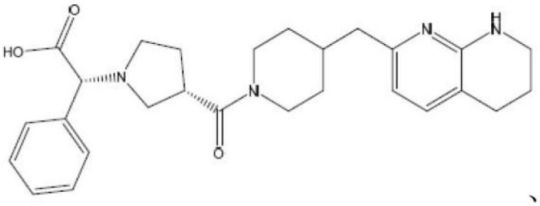
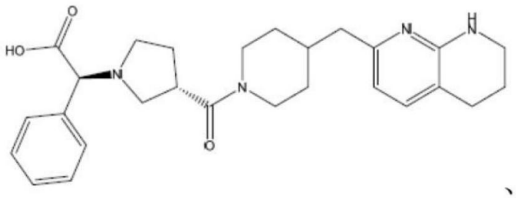
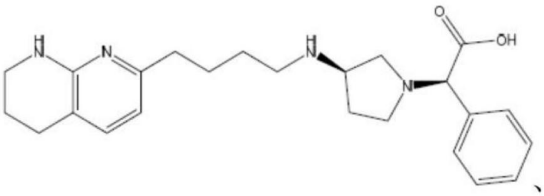
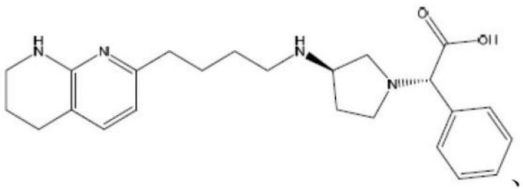
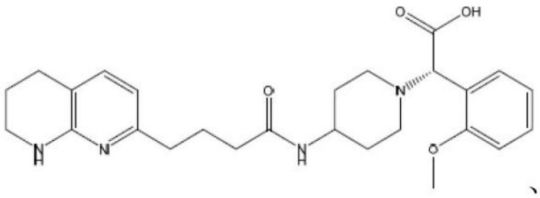
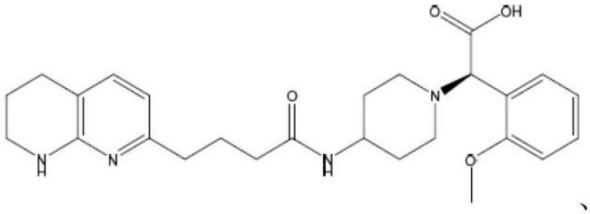
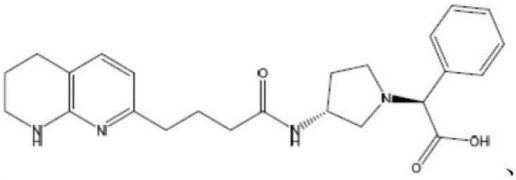

、

、

、

、

和
。

[0180] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

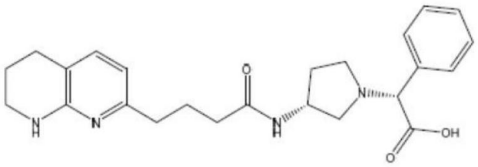
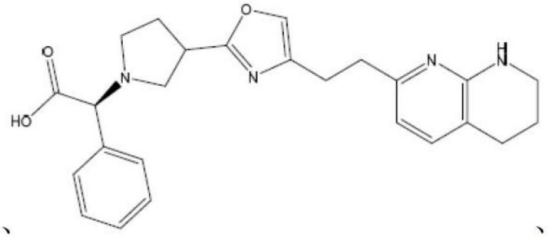
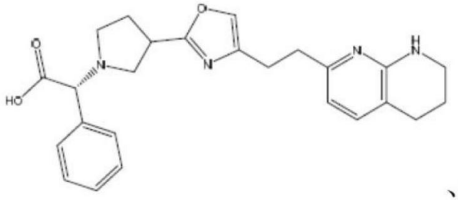
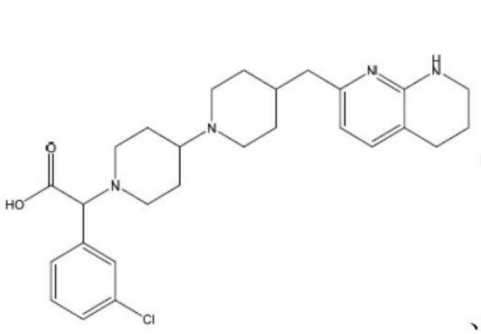
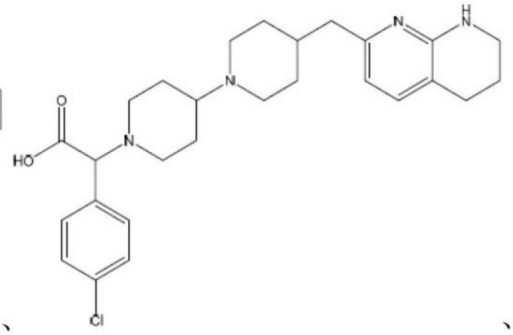

、

、

、

、

、

、

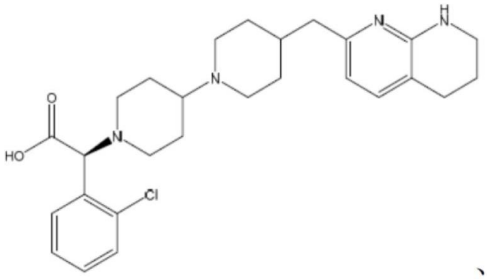
[0181]

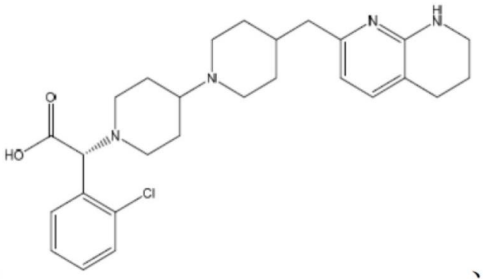

、

、

、

、

、

、

、

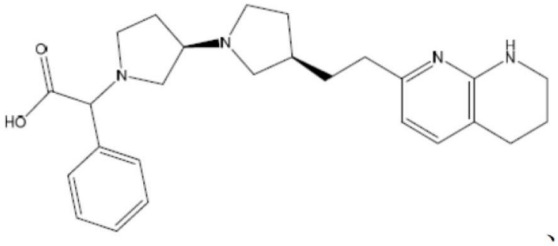

、

、

、

、

、

、


、

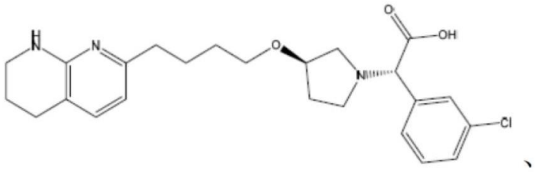
[0182]

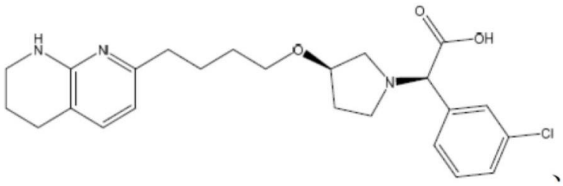

、

、

、

、

、

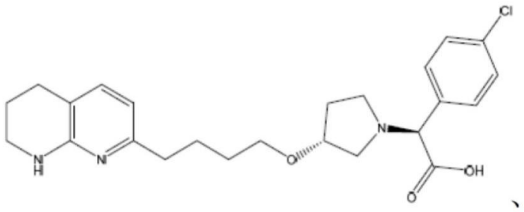




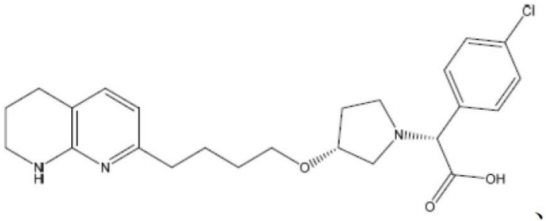


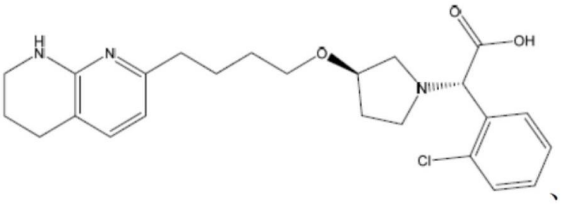


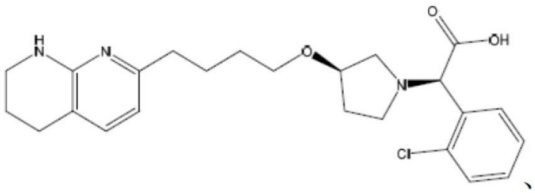


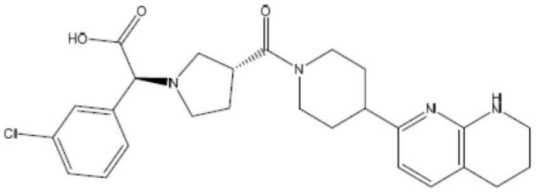


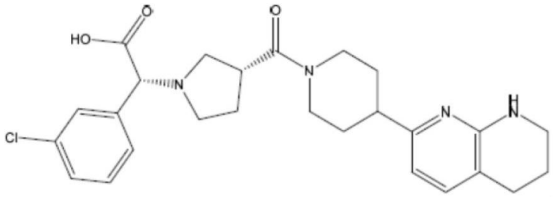
[0183]

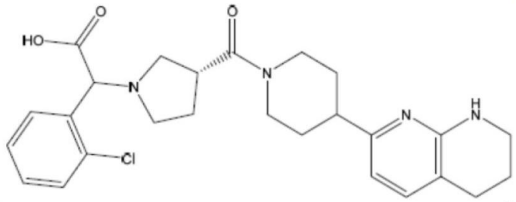


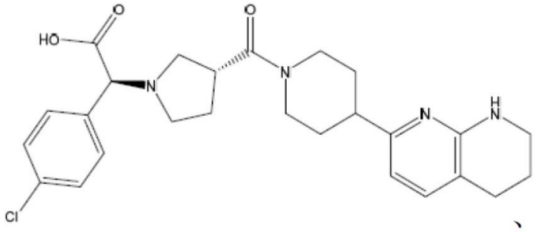


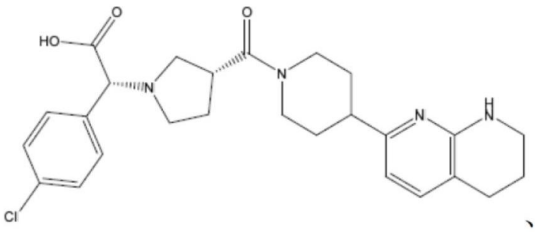


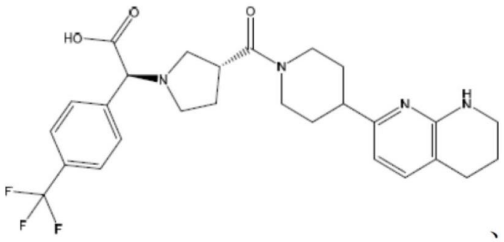
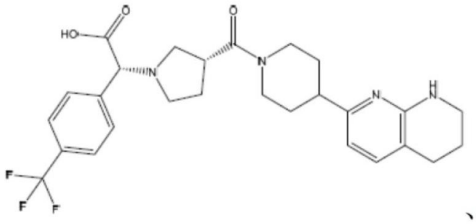
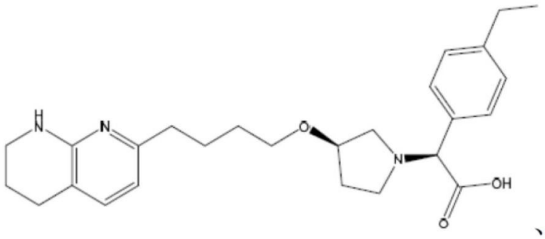
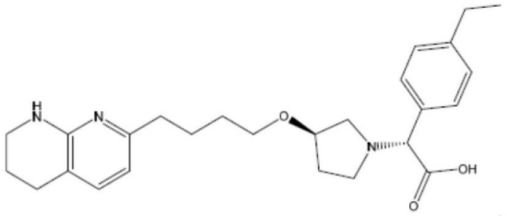
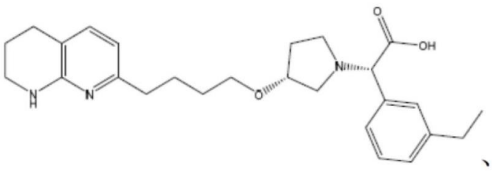
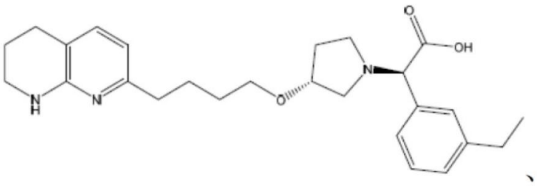
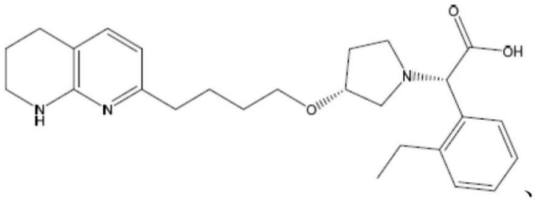
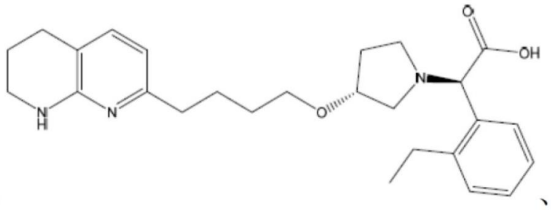
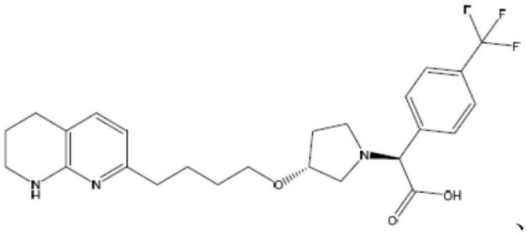
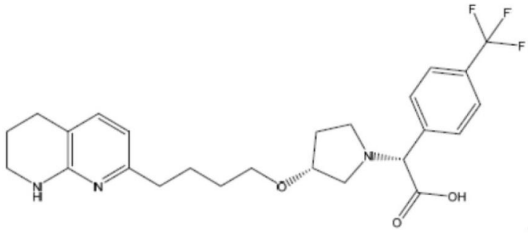
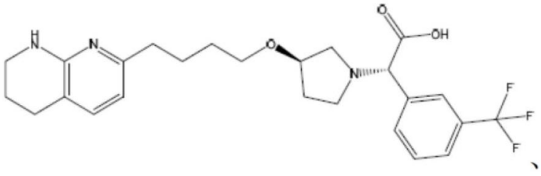
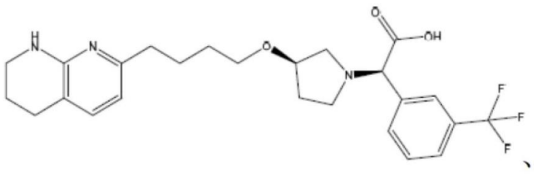
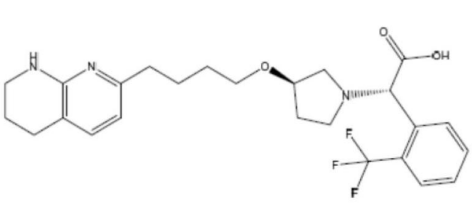
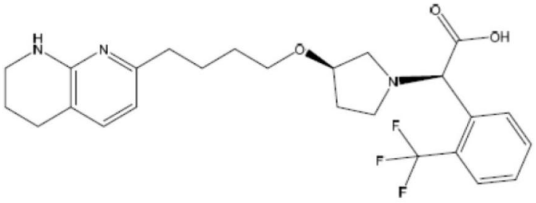




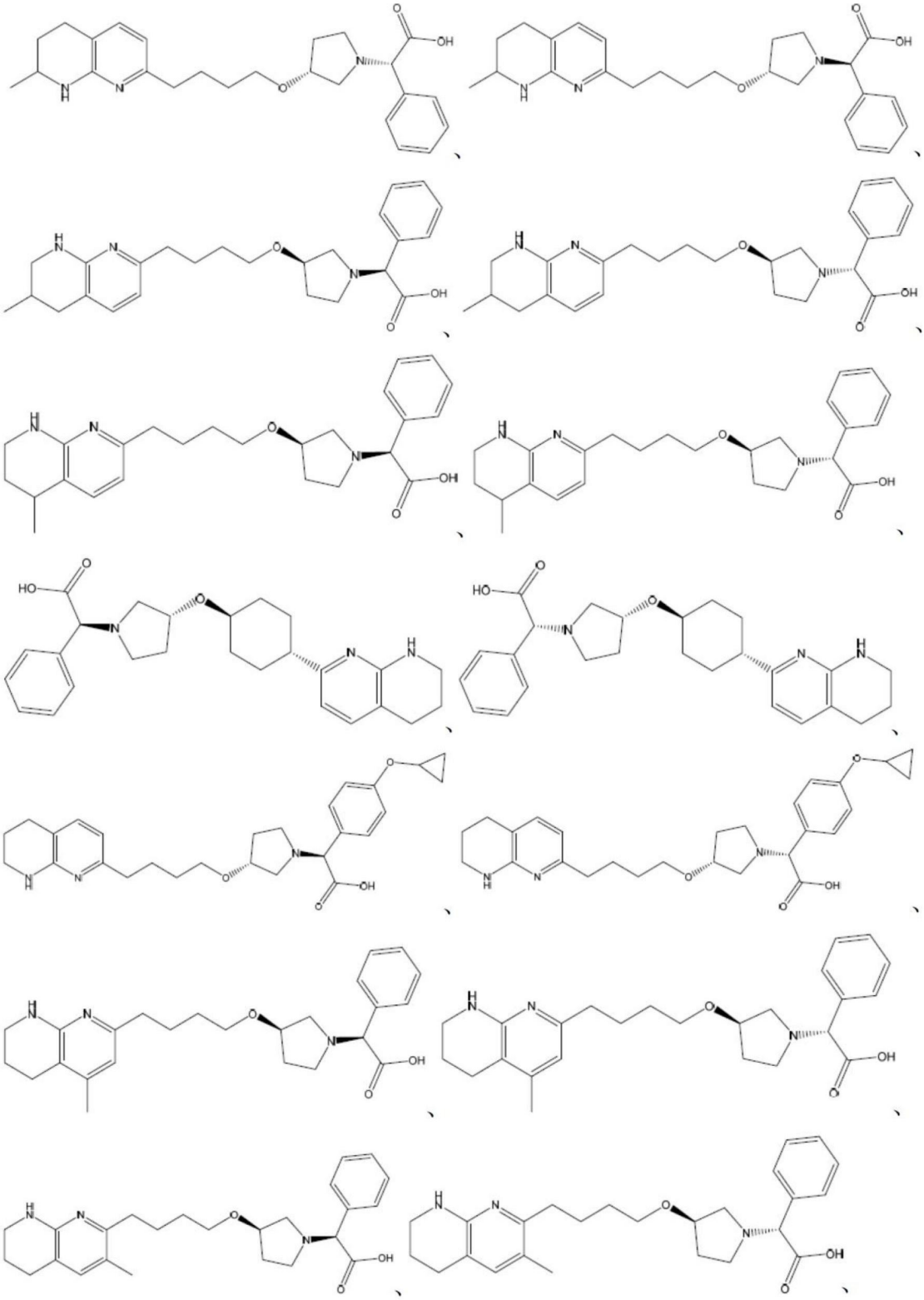






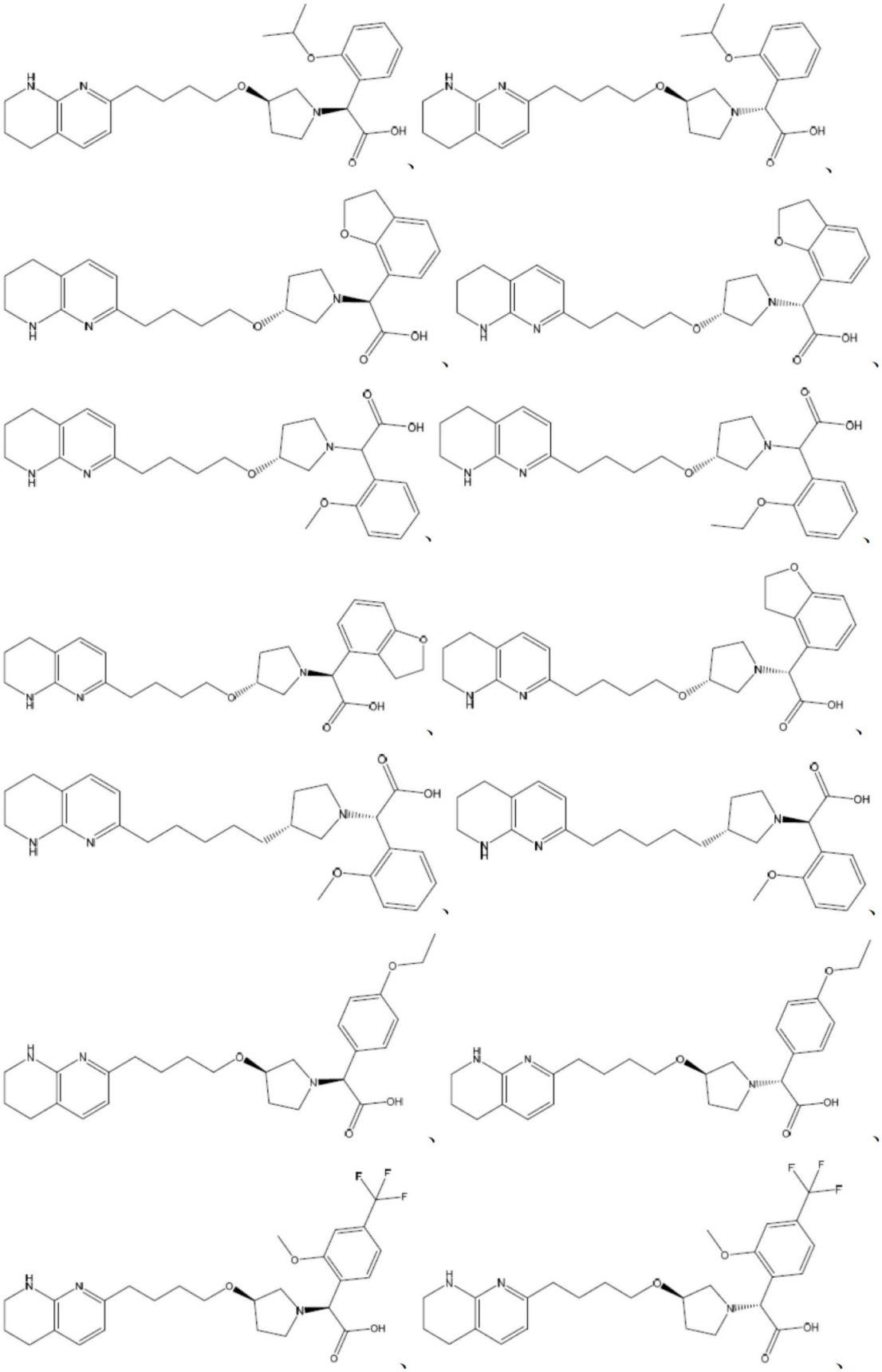
[0184]  、  、  、  、  、  、  、  、  、  、  、  、  和  。

[0185] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

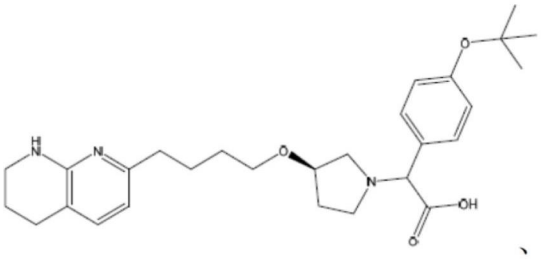


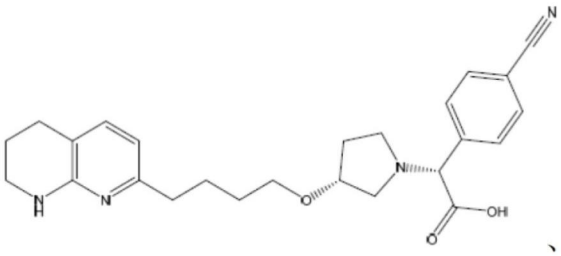
[0186]

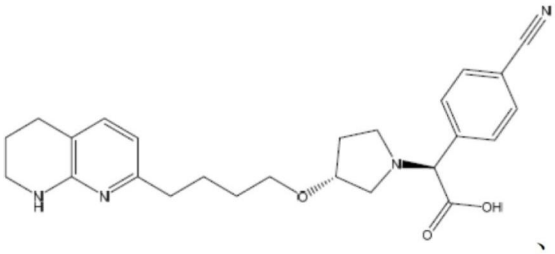
[0187]

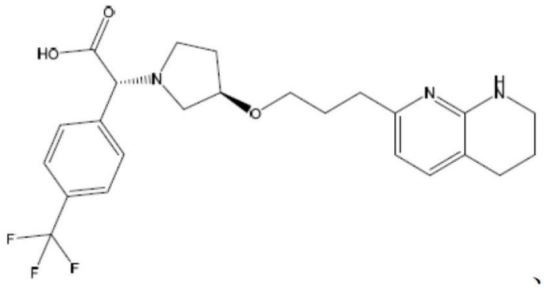


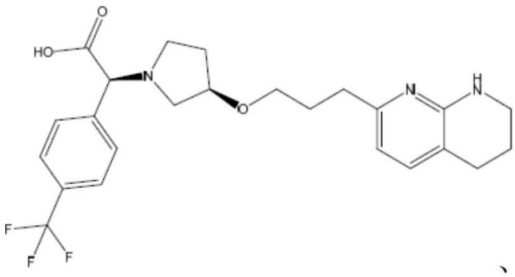
[0188]

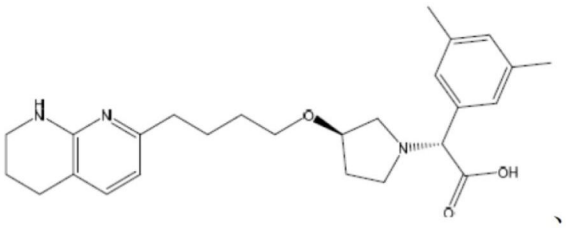


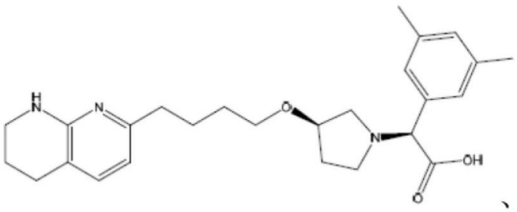


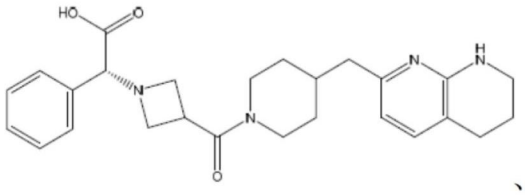


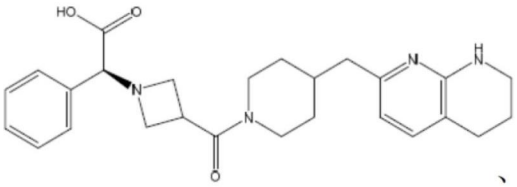


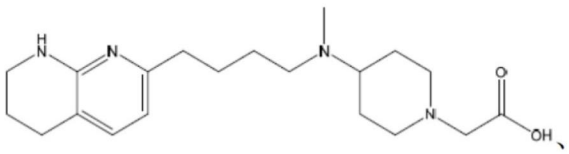


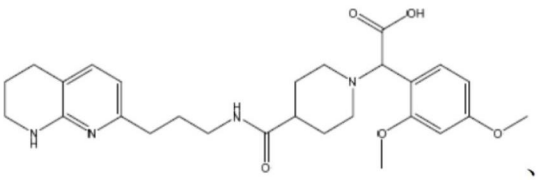


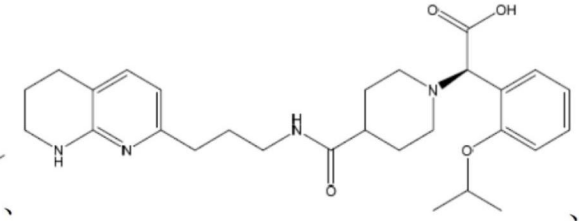




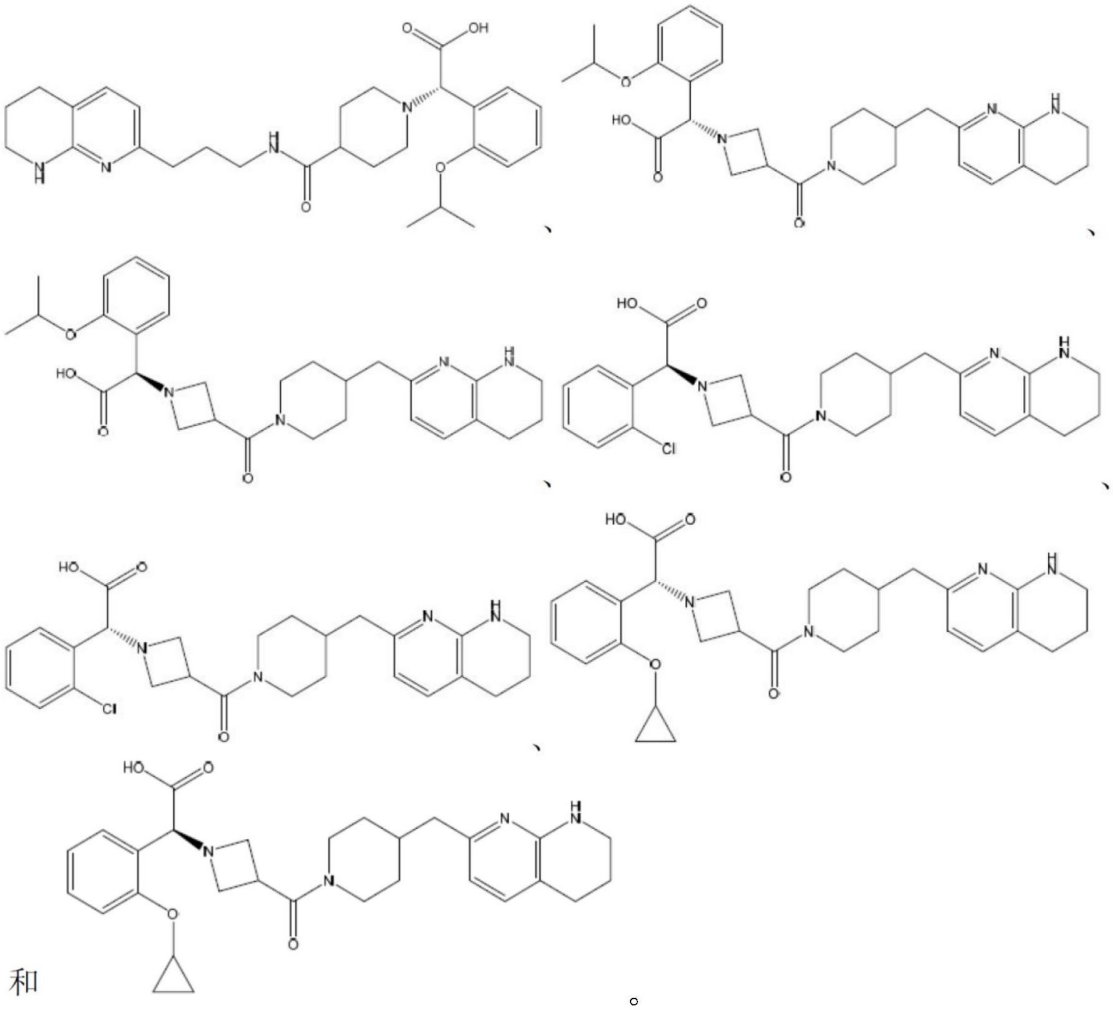








[0189]

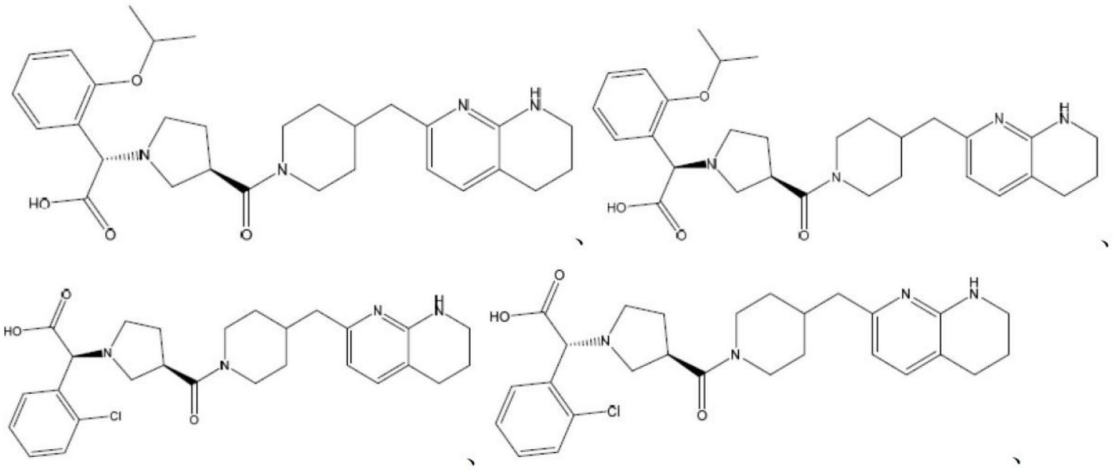


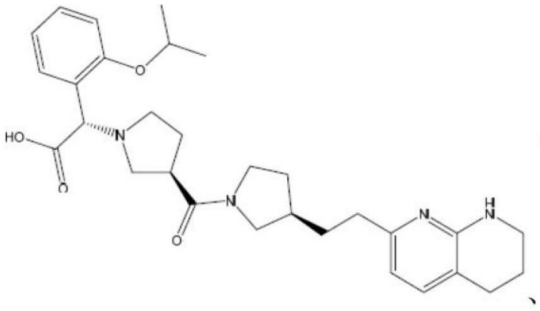
和

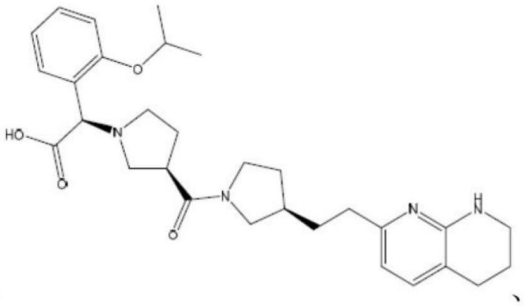
。

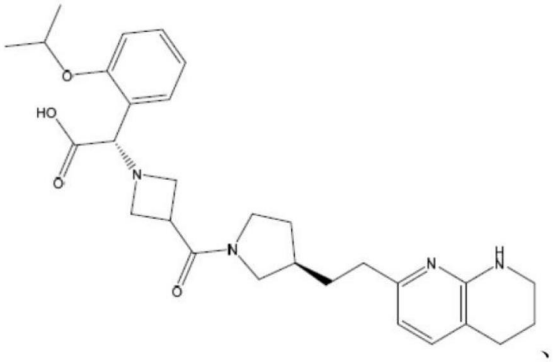
[0190] 在某些实施例中，本发明涉及选自由以下组成的群组的化合物：

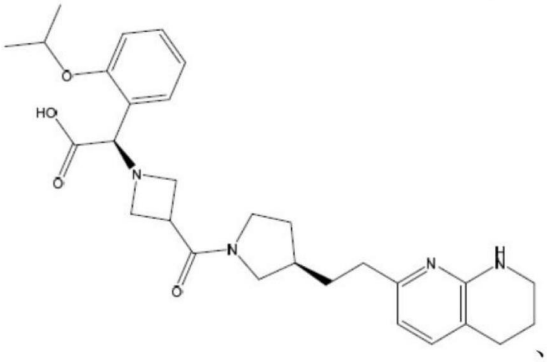
[0191]



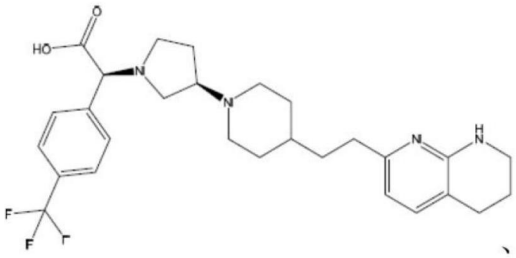


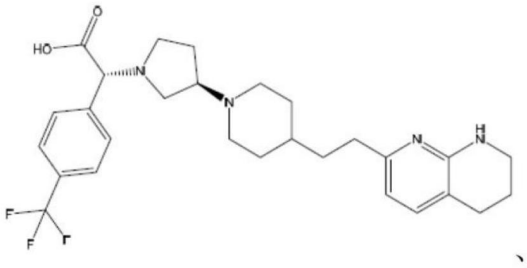


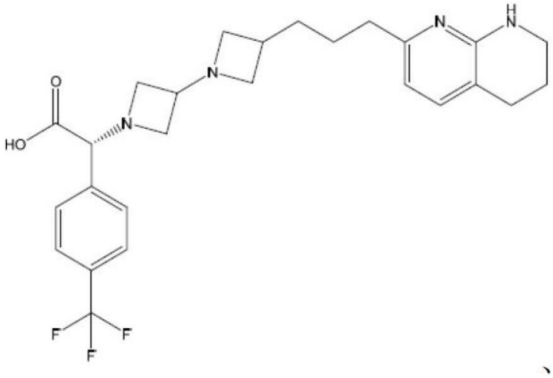


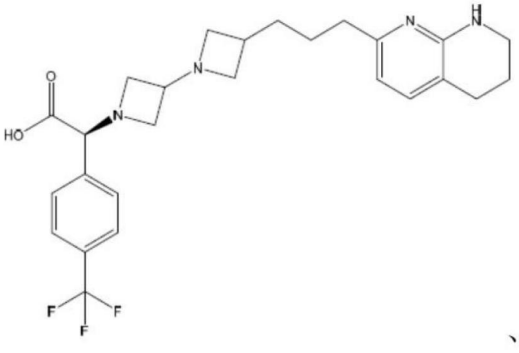


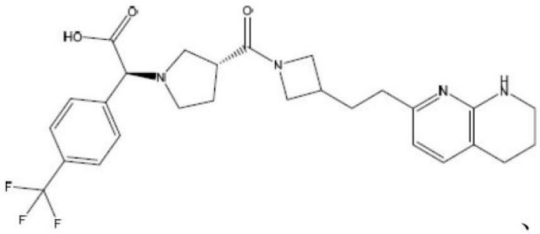
[0192]

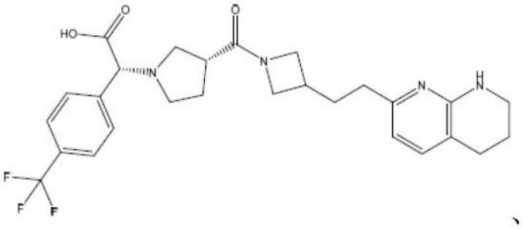


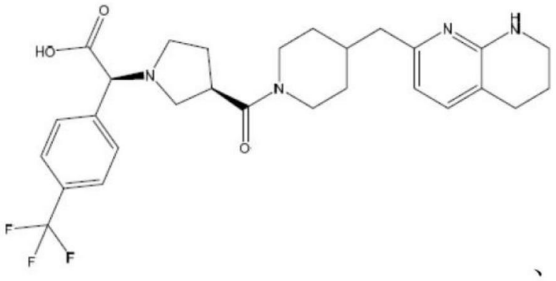
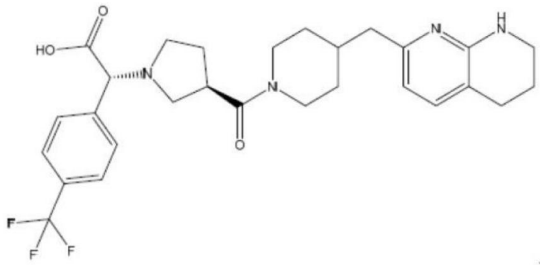
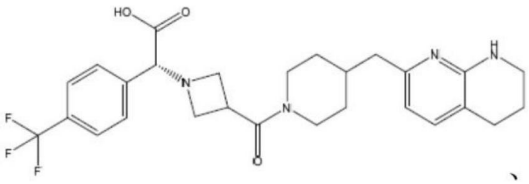
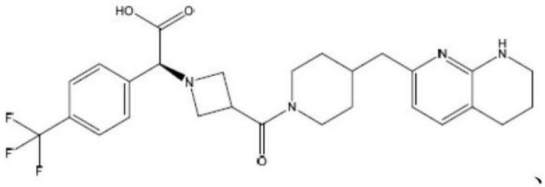
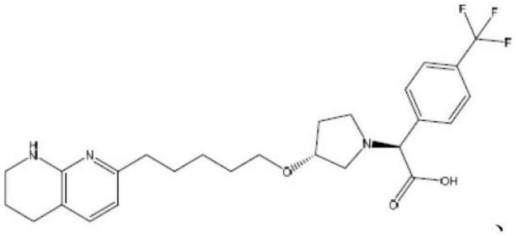
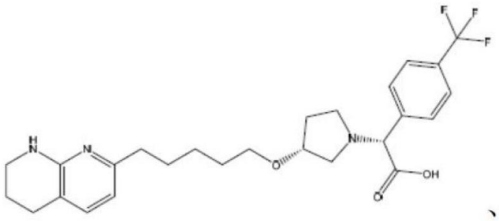




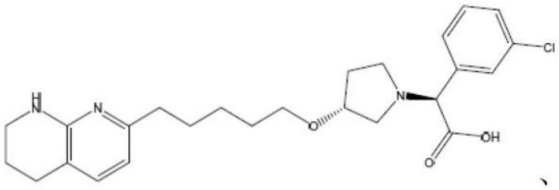
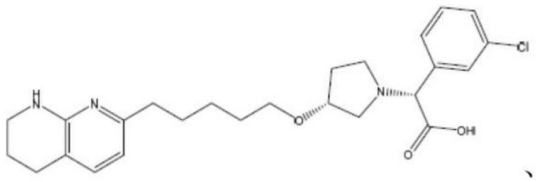
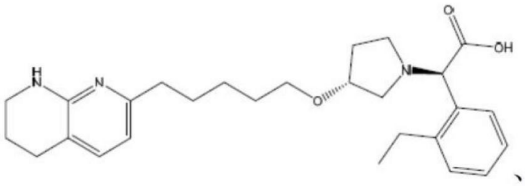
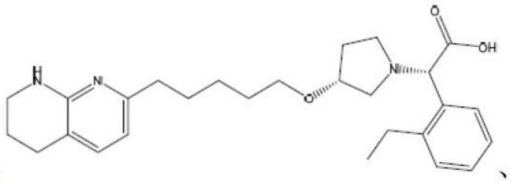
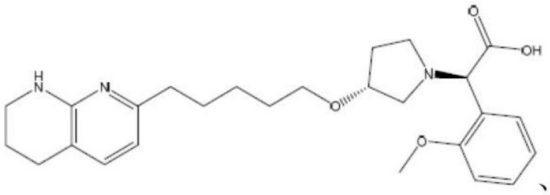
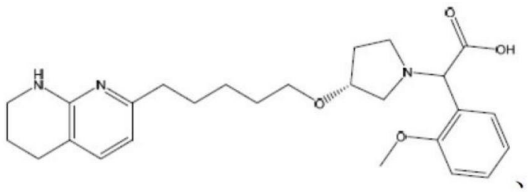
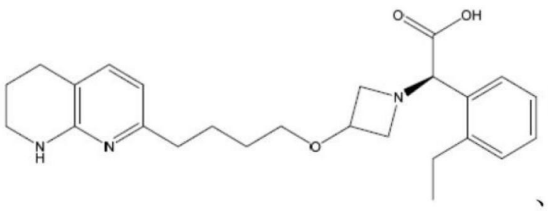
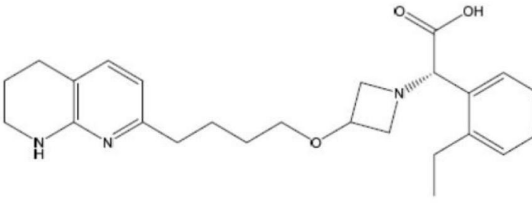


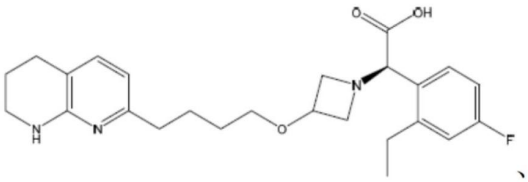
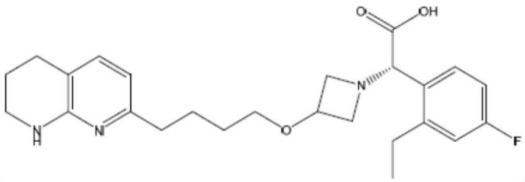
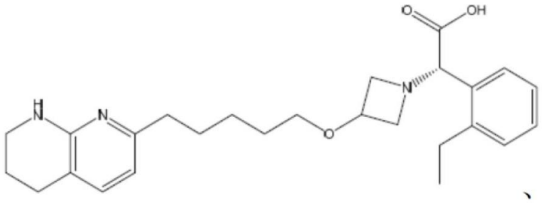
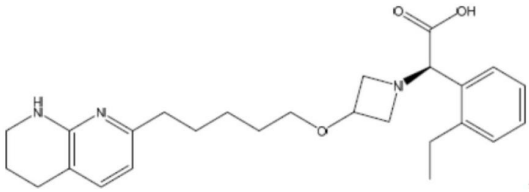
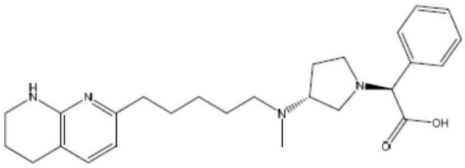
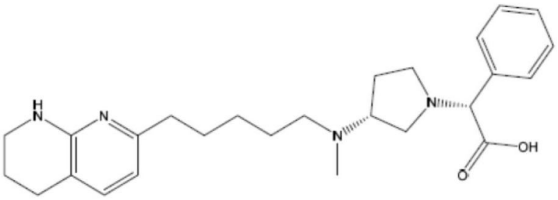





、

、

、

、

、

、

[0193]


、

、

、

、

、

、

、

、

[0194]  、  、  、  、  和  。

[0195] 示例性药物组合物

[0196] 在某些实施例中，本发明涉及一种药物组合物，其包含上述化合物中的任一种和药学上可接受的载剂。

[0197] 患者(包括但不限于人类)可通过对所述患者施用有效量的活性化合物或药学上可接受的前药或其盐(在药学上可接受的载剂或稀释剂存在下)进行治疗。活性物质可通过任何适宜途径施用，例如，经口，非经肠、静脉内、皮内、皮下或局部，呈液体或固体形式。

[0198] 药物组合物中的活性化合物的浓度将取决于药物的吸收、失活和排泄速率以及为所属领域的技术人员已知的其它因素。应注意，剂量值也将随着待减轻的病状的严重度变化。应进一步了解，任何特定个体、具体剂量方案应根据个体需求和施用或监督组合物的施用的人的专业判断随时间调整，和本文中所述的浓度范围仅为示例性且不意图限制要求组合物的范围或实务。活性成分可一次施用，或可分成许多更小剂量以在变化的时间间隔施用。

[0199] 在某些实施例中，活性化合物的施用方式为经口。经口组合物一般将包括惰性稀释剂或可食用载剂。可将其封闭于明胶胶囊中或压缩成锭剂。出于经口治疗施用的目的，可将活性化合物与赋形剂并入和呈锭剂、口含锭或胶囊形式使用。可包含医药上兼容的粘合剂和/或辅助物质作为组合物的部分。

[0200] 锭剂、丸剂、胶囊、口含锭等可含有下列成分或类似性质的化合物中的任一种：粘合剂(如微晶纤维素、黄蓍胶或明胶)、赋形剂(如淀粉或乳糖)、崩解剂(如藻酸、淀粉羟基乙酸钠(Primogel)或玉米淀粉)、润滑剂(如硬脂酸镁或Sterote)、助流剂(如胶状二氧化硅)、甜味剂(如蔗糖或糖精)或调味剂(如薄荷、水杨酸甲酯或橙香精)。当单位剂型为胶囊时，除以上类型的物质外，其可含有液体载剂(如脂肪油)。此外，单位剂型可含有修饰剂量单位的实物形态的各种其它物质，例如，糖、虫胶的涂料或其它肠剂。

[0201] 化合物可作为酏剂、悬浮液、糖浆、薄片、咀嚼口香糖等的组分施用。除活性化合物外，糖浆可含有作为甜味剂的蔗糖或甜味剂和某些防腐剂、染料和色素和香料。

[0202] 化合物或药学上可接受的前药或其盐也可与不损害期望作用的其它活性物质或

与补充期望作用的物质(如抗生素、抗真菌剂、消炎药或其它抗病毒剂(包括但不限于核苷化合物))混合。用于非经肠、皮内、皮下或局部施用的溶液或悬浮液可包括下列组分:无菌稀释剂,如注射用水、盐水溶液、固定油、聚乙二醇、甘油、丙二醇或其它合成溶剂;抗菌剂,如苄醇或对氧苯甲酸甲酯;抗氧化剂,如抗坏血酸或亚硫酸氢钠;螯合剂,如乙二胺四乙酸;缓冲剂,如乙酸盐、柠檬酸盐和磷酸盐,和渗透调节剂,如氯化钠或右旋糖。可将亲本制剂封闭于安瓿、一次性注射器或由玻璃或塑料制得的多剂量小瓶中。

[0203] 如果静脉内施用,则载剂包括生理盐水和磷酸盐缓冲盐水(PBS)。

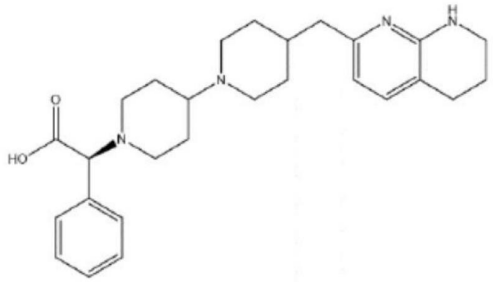
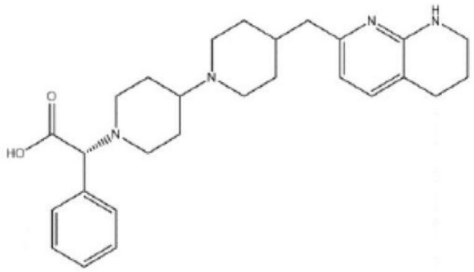
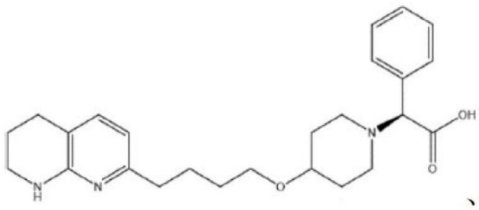
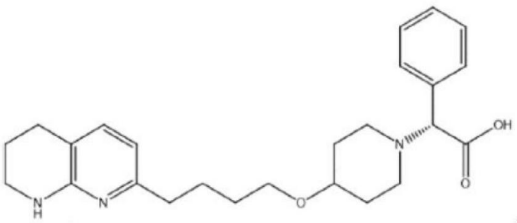
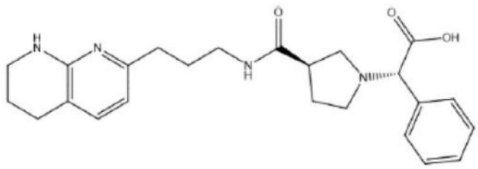
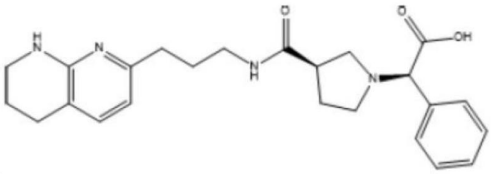
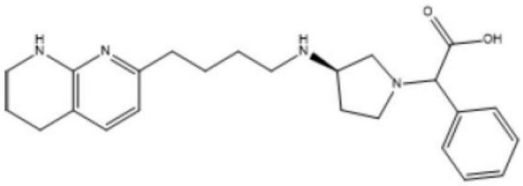
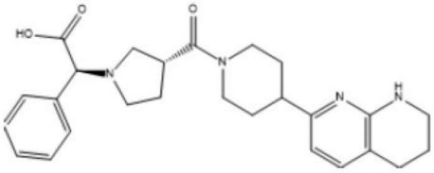
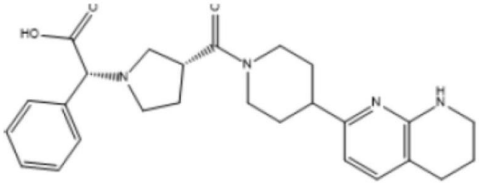
[0204] 在某些实施例中,利用将保护化合物免于自身体快速消除的载剂制备活性化合物,如控制释放调配物,其包括但不限于植入物和微胶囊递送系统。可使用可生物降解、生物兼容性聚合物,如乙烯乙酸乙烯酯、聚酐、聚乙醇酸、胶原蛋白、聚原酸酯和聚乳酸。例如,肠包膜化合物可用于保护免于胃酸的裂解。这些调配物的制备方法对所属领域的技术人员将为显而易见的。适宜物质也可市面上获得。

[0205] 脂质体悬浮液(包括但不限于靶向具有对病毒抗原的单株抗体的感染细胞的脂质体)也优选地作为药学上可接受的载剂。可根据为所属领域的技术人员已知方法(例如,如在美国专利第4,522,811号(以引用方式并入)中所述)制备这些。例如,可通过以下制备脂质体调配物:将适宜脂质(如硬脂酰磷脂酰乙醇胺、硬脂酰磷脂酰胆碱和胆固醇)溶解于无机溶剂中,然后蒸发溶剂,后面在容器的表面留下干燥脂质的薄膜。然后将活性化合物的水溶液引入所述容器中。然后将所述容器用手涡旋以将脂质物质自容器的侧面释放并使脂质聚集体分散,从而形成脂质体悬浮液。

[0206] 本发明的示例性方法

[0207] 在某些实施例中,本发明涉及一种治疗选自由以下组成的群组的疾病或病状的方法:特发性肺纤维化、糖尿病性肾病、局部区段性肾小球硬化症、慢性肾病、非酒精性脂肪性肝炎、原发性胆管炎、原发性硬化性胆管炎、实体肿瘤、血液肿瘤、器官移植、奥尔波特综合症、间质性肺病、辐射诱导型纤维化、博来霉素诱导型纤维化、石棉诱导型纤维化、流感诱导型纤维化、凝血诱导型纤维化、血管损伤诱导型纤维化、主动脉狭窄和心肌纤维化,所述方法包括以下步骤:对有需要的个体施用治疗上有效量的上述化合物中的任一种。

[0208] 在某些实施例中,所施用的化合物选自由以下组成的群组:

[0209]  、  、  、  、  、  、  、  和  。

[0210] 在某些实施例中，本发明涉及上述方法中的任一种，其中所述疾病或病状为实体肿瘤(肉瘤、癌和淋巴瘤)。可根据本发明治疗的示例性肿瘤包括(例如)尤因氏肉瘤(Ewing's sarcoma)、横纹肌肉瘤、骨肉瘤、骨髓肉瘤、软骨肉瘤、脂肪肉瘤、平滑肌肉瘤、软组织肉瘤、非小细胞肺癌、小细胞肺癌、支气管癌、前列腺癌、乳腺癌、胰腺癌、胃肠癌、结肠癌(colon cancer)、直肠癌、结肠癌瘤(colon carcinoma)、结肠直肠腺瘤、甲状腺癌、肝癌、肝内胆管癌、肝细胞癌、肾上腺癌、胃癌(stomach cancer)、胃癌(gastric cancer)、神经胶质瘤(例如，成人、儿童脑干、儿童大脑星形细胞瘤、儿童视觉通路和下丘脑)、胶质母细胞瘤、子宫内膜癌、黑色素瘤、肾癌、肾盂癌、膀胱癌、子宫体、子宫颈癌、阴道癌、卵巢癌、多发性骨髓瘤、食管癌、脑癌(例如，脑干神经胶质瘤、小脑星形细胞瘤、大脑星形细胞瘤/恶性神经胶质瘤、室管膜瘤、髓母细胞瘤、幕上原始神经外胚层肿瘤、视觉通路和下丘脑神经胶质瘤)、唇和口腔和咽、喉、小肠、黑色素瘤、绒毛状结肠腺瘤、瘤形成、上皮性瘤形成、淋巴瘤(例如，AIDS-相关、伯基特氏(Burkitt's)、皮肤T-细胞、霍奇金氏(Hodgkin)、非霍奇金氏和原发性中枢神经系统)、乳腺癌、基底细胞癌、鳞状细胞癌、光化性角化病、包含实体肿瘤的肿瘤疾病、颈部或头部的肿瘤、真性红细胞增多症、特发性血小板增多症、伴有骨髓组织变形的骨髓纤维化、沃尔登斯特氏巨球蛋白血症(Waldenstrom'smacroglobulinemia)、肾上腺皮质

癌、AIDS-相关癌症、儿童小脑星形细胞瘤、肝外胆管癌、恶性纤维组织细胞瘤、骨癌、支气管腺瘤/类癌、类癌瘤、胃肠类癌瘤、原发性中枢神经系统、小脑星形细胞瘤、儿童癌症、颅外生殖细胞瘤、性腺外生殖细胞瘤、眼内黑色素瘤眼癌、视网膜母细胞瘤眼癌、胆囊癌、生殖细胞肿瘤(例如,颅外、性腺外和卵巢)、妊娠滋养细胞肿瘤、肝细胞癌、下咽癌、下丘脑和视觉通路神经胶质瘤、胰岛细胞癌(内分泌胰脏)、喉癌、骨的恶性纤维组织细胞瘤/骨肉瘤、间皮瘤、原发隐匿的转移性鳞状颈癌、多发性内分泌瘤形成综合症、多发性骨髓瘤/浆细胞肿瘤、蕈状肉芽肿、鼻腔和鼻窦癌、鼻咽癌、神经母细胞瘤、口癌、口咽癌、卵巢上皮癌、卵巢生殖细胞肿瘤、卵巢低恶性潜能肿瘤、胰岛细胞胰腺癌、甲状旁腺癌、嗜铬细胞瘤、松果体母细胞瘤、垂体瘤、胸膜肺母细胞瘤、输尿管移行细胞癌、视网膜母细胞瘤、唾腺癌、塞扎里综合症(Sezary syndrome)、非黑色素瘤皮肤癌、梅克尔(Merkel)细胞癌、睾丸癌、胸腺瘤和威尔姆氏肿瘤(Wilms'tumor)。

[0211] 在某些实施例中,本发明涉及上述方法中的任一种,其中所述疾病或病状为血液肿瘤。可根据本发明治疗的示例性血液肿瘤包括(例如)急性淋巴细胞性白血病、急性骨髓性白血病、慢性淋巴细胞性白血病、慢性骨髓性白血病、霍奇金氏淋巴瘤、非霍奇金氏淋巴瘤和多发性骨髓瘤。

[0212] 在某些实施例中,本发明涉及上述方法中的任一种,其中所述疾病或病状选自由以下组成的群组:特发性肺纤维化、与间质性肺病相关联的全身性硬化症、与间质性肺病相关联的肌炎、与间质性肺病相关联的全身性红斑狼疮,和与间质性肺病相关联的类风湿性关节炎。

[0213] 在某些实施例中,本发明涉及上述方法中的任一种,其中所述疾病或病状选自由以下组成的群组:糖尿病性肾病、局部区段性肾小球硬化和慢性肾病。

[0214] 在某些实施例中,本发明涉及上述方法中的任一种,其中所述疾病或病状选自由以下组成的群组:非酒精性脂肪性肝炎、原发性胆管炎和原发性硬化性胆管炎。

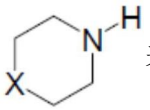
[0215] 在某些实施例中,本发明涉及上述方法中的任一种,其中所述个体为哺乳动物。在某些实施例中,本发明涉及上述方法中的任一种,其中所述个体为人类。

[0216] 实例

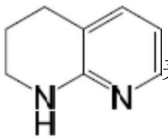
[0217] 现在大体上描述本发明,其将通过参考下列实例更容易理解,包含所述实例仅出于说明本发明的某些方面和实施例的目的,且不意图限制本发明。

[0218] 制备本发明化合物的一般反应图和程序

[0219] 基团R和R_1为适宜酯保护基团;R_2、R_3、R_4、R_5和R_6为H或适宜取代基;且L为适宜连接基。

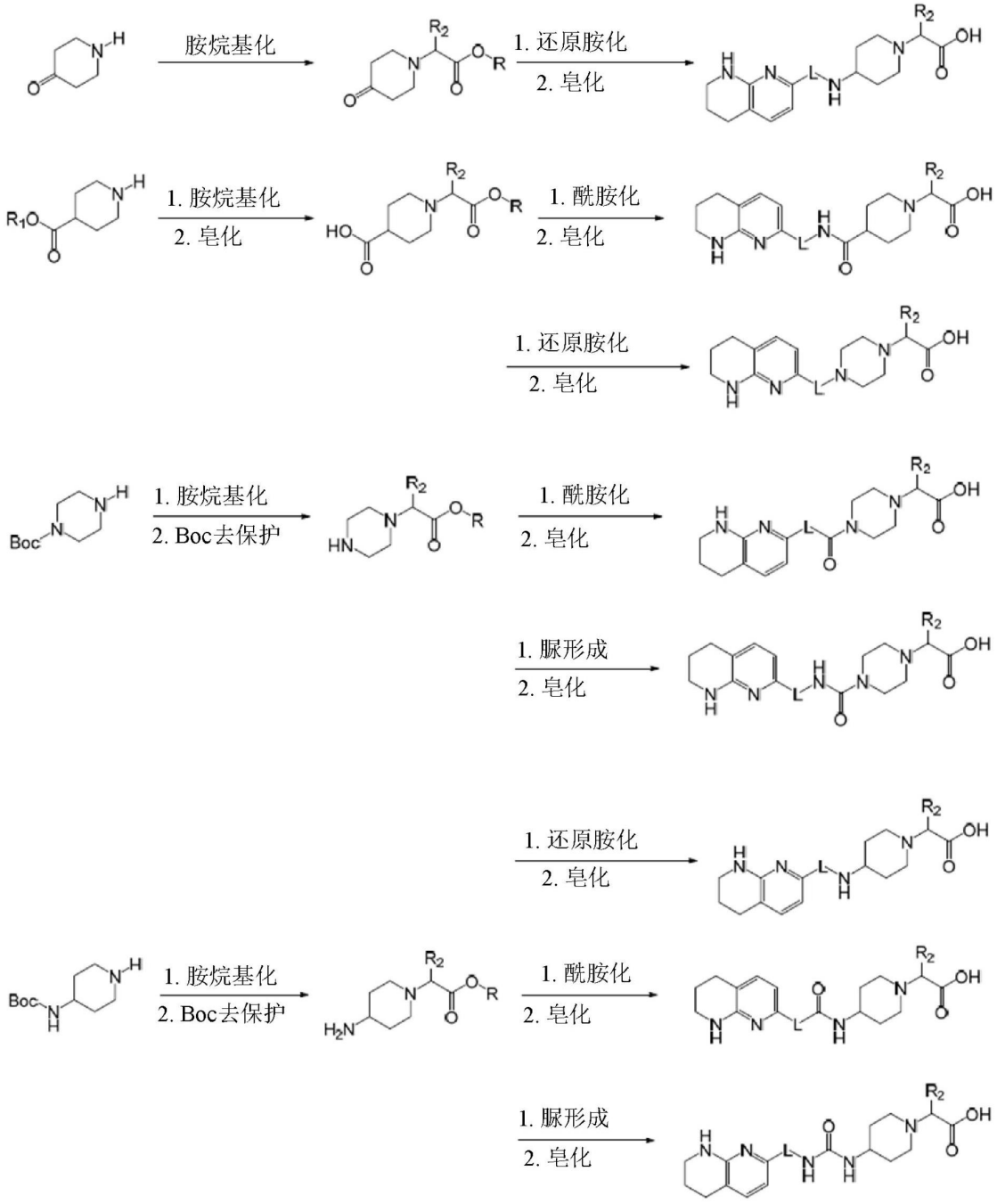
[0220] 

表示适宜任选经取代的3至12元杂环亚烷基,其包括哌啶、哌嗪、哌嗪酮、吡咯烷和氮杂环丁烷。

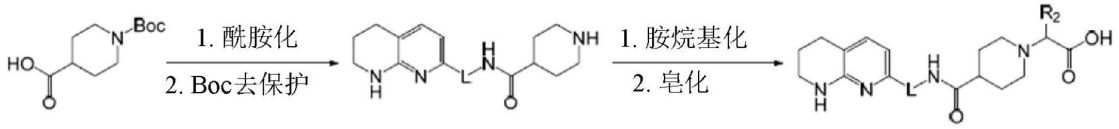
[0221] 

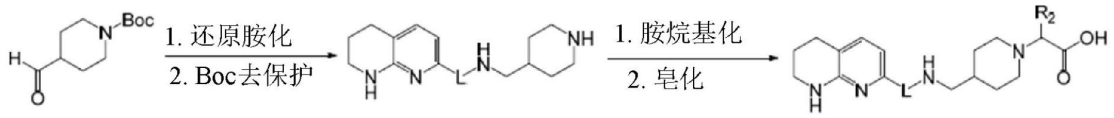
表示适宜任选经取代的四氢萘啶或2-氨基吡啶。

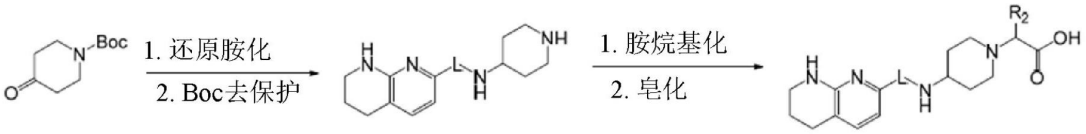
[0222] 合成αvβ6抑制剂的一般反应图

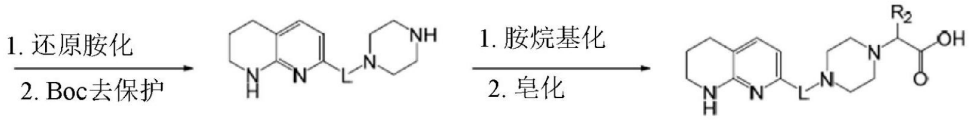

胺烷基化
1. 还原胺化
2. 皂化
1. 胺烷基化
2. 皂化
1. 酰胺化
2. 皂化
1. 还原胺化
2. 皂化
1. 胺烷基化
2. Boc去保护
1. 酰胺化
2. 皂化
1. 脲形成
2. 皂化
1. 还原胺化
2. 皂化
1. 胺烷基化
2. Boc去保护
1. 酰胺化
2. 皂化
1. 脲形成
2. 皂化

[0223]

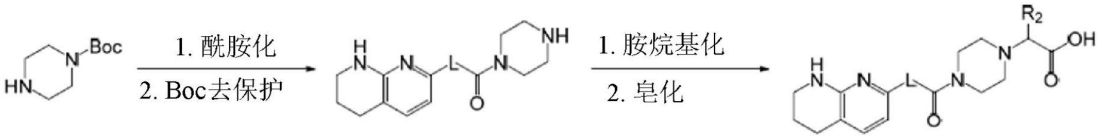


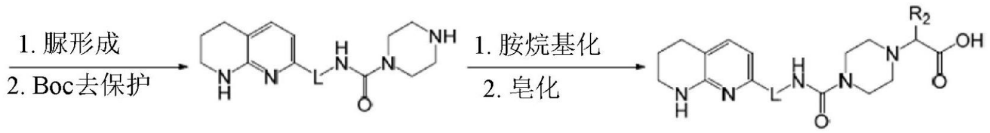


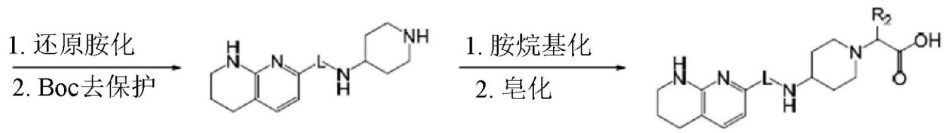


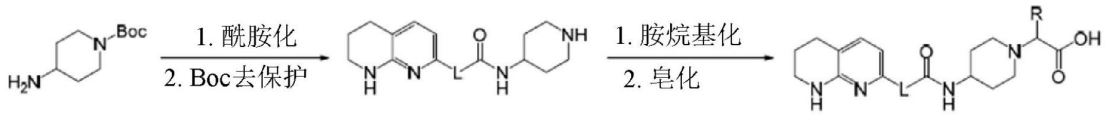


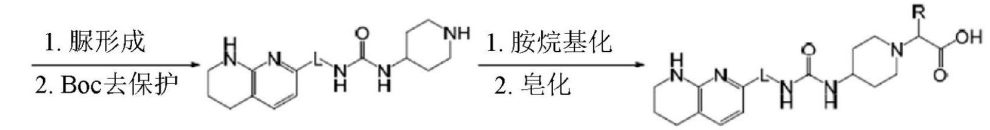
[0224]











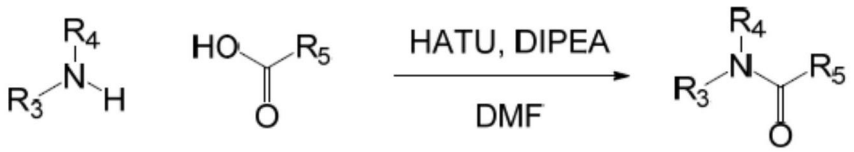
[0225] 一般程序

[0226] 还原胺化：

[0227]

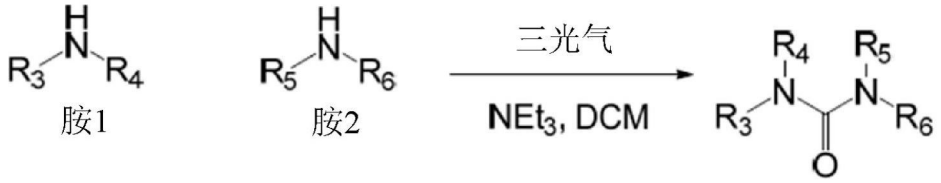
[0228] 将含于DCM或DCE(5至10mL/mmol胺)中的胺(1当量)、醛或酮(1至1.2当量)、NaBH(OAc)$_3$(2至3当量)和HCl或乙酸(0.1至2当量)的混合物在室温下搅拌1至16小时直至通过LC/MS完成。将反应于真空中浓缩或处理(用水稀释和用DCM萃取;将合并的萃取物经Na_2SO_4干燥,过滤和浓缩),和将残余物通过硅胶柱纯化以得到所需胺产物。

[0229] 酰胺键形成：

[0230] 

[0231] 将含于DMF或DCM(5至10mL/mmol胺)中的羧酸(1当量)、胺(0.5至2当量)、HATU(1至2当量)和DIEA(2至5当量)的混合物在室温下搅拌16小时或直至通过LC/MS完成。将反应于真空中浓缩，和将残余物通过硅胶柱纯化以得到所需酰胺产物。

[0232] 脲形成：

[0233] 

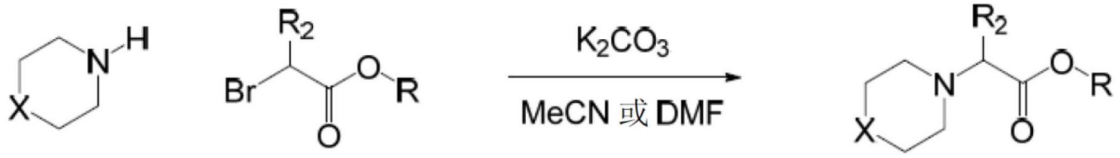
[0234] 在0℃下，向含于DCM(5至10mL/mmol胺1)中的胺1(1当量)和三乙胺(3至5当量)的溶液中添加三光气(0.4至0.5当量)。将反应搅拌30分钟至1小时，和然后添加含于DCM(1至2mL/mmol胺1)中的胺2(0.5至1.5当量)。将反应在室温下搅拌2至16小时，然后在真空下浓缩。将残余物通过硅胶柱纯化以得到所需脲。

[0235] Boc去保护：

[0236] 

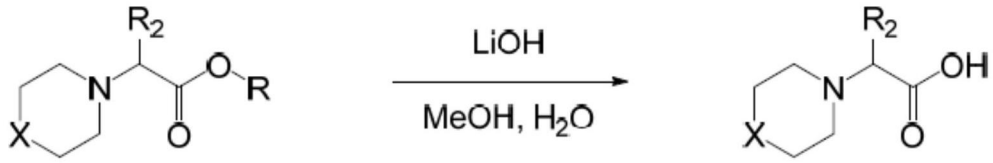
[0237] 在室温下，将Boc-保护的胺(1当量)用含于二噁烷(5至20mL/mmol胺)中的HCl(5至20当量)处理1至4小时。将反应于真空中浓缩，和以粗制物或通过硅胶柱纯化后使用所述胺产物。

[0238] 胺烷基化：

[0239] 

[0240] 将含于MeCN或DMF(3至10mL/mmol胺)中的胺(1当量)、溴乙酸酯(1至1.5当量)和K_2CO_3(2至5当量)的混合物在室温下搅拌4至16小时。将反应于真空中浓缩，和将残余物通过硅胶柱纯化以得到所需氨基乙酸。

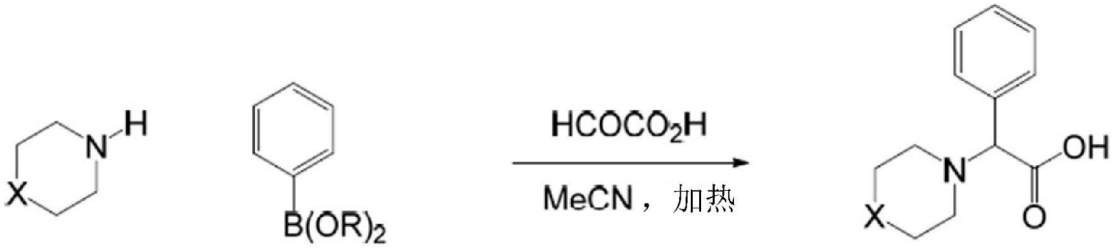
[0241] 皂化：

[0242] 

[0243] 在室温下，将酯(1当量)用含于MeOH(3至10mL/mmol酯)和水(3至10mL/mmol酯)中的LiOH-H_2O(3至5当量)处理1至16小时。将反应于真空中浓缩，和将残余物通过制备型HPLC

纯化以得到所需羧酸产物。

[0244] Petasis反应：

[0245] 

[0246] 作为胺烷基化/皂化顺序的替代，Petasis反应可用于制备某些芳基类似物：在50至80℃下，将含于MeCN或DMF(2至10mL/mmol胺)中的胺(1eq.)、芳基二羟基硼酸或芳基二羟基硼酸酯(1至1.5eq.)和2-氧代基乙酸(1.5至2当量)的混合物搅拌2至16小时。将反应于真空中浓缩，和将残余物通过制备型HPLC纯化以得到所需氨基乙酸。

[0247] 分析方法

[0248] LCMS分析方法

[0249] 使用LC/MS条件，以在214nm和254nm处监测的UV检测器，和以ESI+电离模式扫描110至800amu的质谱，分析最终化合物。

[0250] LC/MS A：柱：XBridge C18，4.6X 50mm，3.5μm；流动相：A水(10mM碳酸氢铵)，B CH_3CN；梯度：5％至95％B于1.4min内，然后保持1.6min；流率：1.8mL/min；烘箱温度50℃。

[0251] LC/MS B：柱：SunFire C18，4.6X 50mm，3.5μm；流动相：A水(0.01％TFA)，B CH_3CN；梯度：5％至95％B于1.5min内，然后保持1.5min；流率：2.0mL/min；烘箱温度50℃。

[0252] LC/MS C：柱：XBridge C18，4.6X 50mm，3.5μm；流动相：A水(10mM碳酸氢铵)，B CH_3CN；梯度：5％至95％B于1.5min内，然后保持1.5min；流率：1.8mL/min；烘箱温度50℃。

[0253] LC/MS D：柱：Poroshell 120EC-C138，4.6X 30mm，2.7μm；流动相：A水(0.01％TFA)，B CH_3CN(0.01％TFA)；梯度：5％至95％B于1.2min分钟内，然后保持1.8min；流率：2.2mL/min；烘箱温度50℃。

[0254] LC/MS E：柱：XBridge C18，3.0X 30mm，2.5μm；流动相：A水(10mM碳酸氢铵)，B CH_3CN；梯度：5％至95％B于1.5min内，然后保持0.6min；流率：1.5mL/min；烘箱温度50℃。

[0255] LC/MS F：柱：Agilent poroshell 120EC-C18，4.6x 50mm，2.7μm：A水(0.1％甲酸)，B CH_3CN(0.1％甲酸)；梯度5％至95％B于4.0min内，然后保持6.0min；流率0.95mL/min；烘箱温度50℃。

[0256] 制备型-HPLC方法

[0257] 将粗制样品溶解于MeOH中和通过制备型HPLC使用Gilson 215仪器(检测波长214nm)纯化：

[0258] 制备型HPLC A：柱：XBridge C18，21.2*250mm，10μm；流动相：A水(10mM碳酸氢铵)，B CH_3CN；如文中的梯度洗脱；流率：20mL/min。

[0259] 制备型HPLC B：柱：XBridge C18，21.2*250mm，10μm；流动相：A水(10mM甲酸)，B CH_3CN；如文中的梯度洗脱；流率：20mL/min。

[0260] 制备型HPLC C：柱：XBridge OBD C18，19*100mm，5μm；流动相：A水，B CH_3CN；如文中的梯度洗脱；流率：20mL/min。

[0261] 制备型手性SFC方法

[0262] 通过手性制备型SFC使用SFC-80(Thar,Waters)仪器(检测波长214nm)将外消旋产物分离成个别对映异构体：

[0263] 制备型手性SFC A:柱:(R,R)-Whelk-O1,20*250mm,5μm(Decial),柱温度:35℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液)＝60/40,流率:80g/min,背压:100巴。

[0264] 制备型手性SFC B:柱:AD 20*250mm,10μm(Daicel),柱温度:35℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液)＝60/40,流率:80g/min,背压:100巴。

[0265] 制备型手性SFC C:柱:AS 20*250mm,10μm(Daicel),柱温度:35℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液)＝60/40,流率:80g/min,背压:100巴。

[0266] 分析型手性SFC方法

[0267] 通过手性SFC使用SFC-80(Thar,Waters)仪器(检测波长214nm)分析手性产物：

[0268] 手性SFC A:柱:(R,R)-Whelk-O1,4.6*100mm,5μm(Decial),柱温度:40℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液),如文中的等浓度洗脱,流率:4g/min,背压:120巴。

[0269] 手性SFC B:柱:AD 4.6*100mm,5μm(Daicel),柱温度:40℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液),如文中的等浓度洗脱,流率:4g/min,背压:120巴。

[0270] 手性SFC C:柱:AS 4.6*100mm,5μm(Daicel),柱温度:40℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液),如文中的等浓度洗脱,流率:4g/min,背压:120巴。

[0271] 手性SFC D:柱:OD 4.6*100mm,5μm(Daicel),柱温度:40℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液),如文中的等浓度洗脱,流率:4g/min,背压:120巴。

[0272] 手性SFC E:柱:Cellulose-SC 4.6*100mm,5μm(Daicel),柱温度:40℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液),如文中的等浓度洗脱,流率:4g/min,背压:120巴。

[0273] 手性SFC F:柱:OZ 4.6*100mm,5μm(Daicel),柱温度:40℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液),如文中的等浓度洗脱,流率:4g/min,背压:120巴。

[0274] 手性SFC G:柱:IC 4.6*100mm,5μm(Daicel),柱温度:40℃,流动相:CO_2/甲醇(0.2%甲醇的氨溶液),如文中的等浓度洗脱,流率:4g/min,背压:120巴。

[0275] 手性SFC H:柱:AD 4.6*250mm,5μm(SHIMADZU),柱温度:40℃,流动相:正己烷(0.1%DEA):EtOH(0.1%DEA),如文中的等浓度洗脱,流率:1mL/min。

[0276] 手性SFC I:柱:IC 4.6*250mm,5μm(SHIMADZU),柱温度:40℃,流动相:正己烷(0.1%DEA):EtOH(0.1%DEA),如文中的等浓度洗脱,流率:1mL/min。

[0277] 手性SFC J:柱:(S,S)-Whelk-O1 4.6*250mm,5μm(SHIMADZU),柱温度:40℃,流动相:正己烷(0.1%DEA):EtOH(0.1%DEA),如文中的等浓度洗脱,流率:1mL/min。

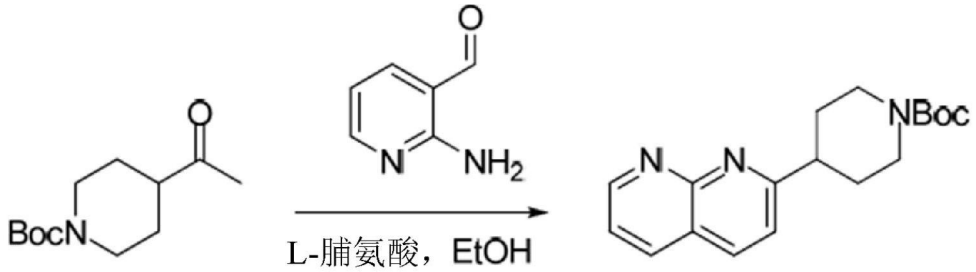
[0278] 手性SFC K:柱:OZ-H 4.6*250mm,5μm(SHIMADZU),柱温度:40℃,流动相:正己烷(0.1%DEA):EtOH(0.1%DEA),如文中的等浓度洗脱,流率:1mL/min。

[0279] 手性SFC L:柱:手性PAK IG 4.6*250mm,5μm(SHIMADZU),柱温度:35℃,流动相:正己烷(0.1%DEA):EtOH(0.1%DEA),如文中的等浓度洗脱,流率:1mL/min。

[0280] 实例1:制备2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-基)乙酸(化合物1)

[0281] 步骤1:4-(1,8-萘啶-2-基)哌啶-1-甲酸叔丁酯

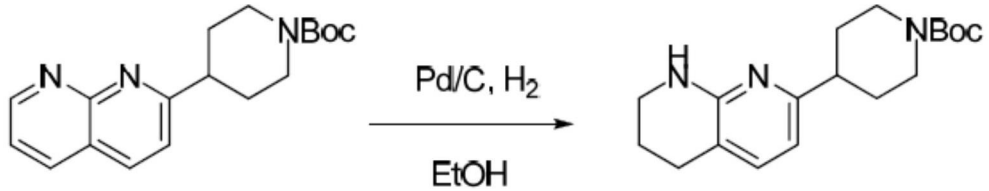
[0282]



[0283] 将含于EtOH(20mL)中的4-乙酰基哌啶-1-甲酸叔丁酯(2.0g,8.80mmol)、2-氨基烟碱醛(1.1g,8.80mmol)和L-脯氨酸(2.0g,17.60mmol)的混合物加热至回流过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc＝1:1)纯化以得到呈无色油的4-(1,8-萘啶-2-基)哌啶-1-甲酸叔丁酯(0.8g)。产率30%(100%纯度,UV＝214nm,ESI 314.2$(M+H)^+$)。

[0284] 步骤2:4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-甲酸叔丁酯

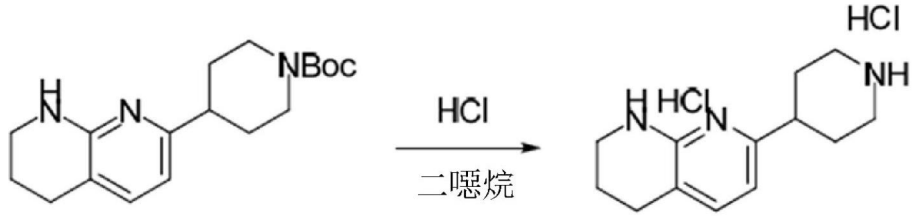
[0285]



[0286] 在气球氢气下,于EtOH(20mL)中,在室温下,将4-(1,8-萘啶-2-基)哌啶-1-甲酸叔丁酯(0.8g,2.56mmol)经Pd-C(100mg,活性碳载10%)氢化过夜。将反应通过硅藻土过滤和浓缩以得到呈无色油的粗制4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-甲酸叔丁酯(800mg),将其直接用于下一步骤。产率98%(95%纯度,UV＝214nm,ESI 318.2$(M+H)^+$)。

[0287] 步骤3:7-(哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶二盐酸盐

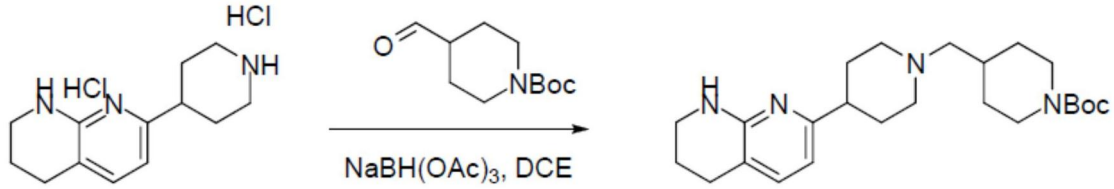
[0288]



[0289] 在室温下,将7-(哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶二盐酸盐(800mg,2.52mmol)用HCl的1,4-二噁烷溶液(4N,4mL)处理2小时。于真空中去除溶剂以得到呈白色固体的粗制7-(哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶二盐酸盐(750mg)。产率95%(100%纯度,UV＝214nm,ESI 218.2$(M+H)^+$)。将粗产物直接用于下个步骤。

[0290] 步骤4:4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-甲酸叔丁酯

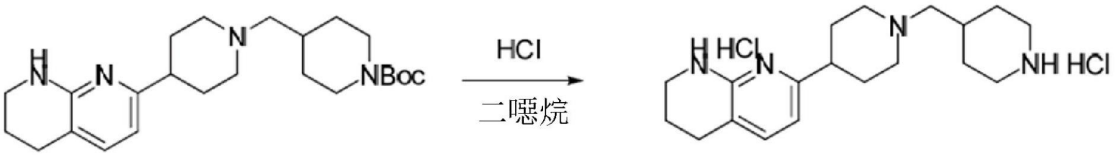
[0291]



[0292] 在氮气氛围下,在室温下,将含于DCE(5mL)中的7-(哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶二盐酸盐(300mg,1.04mmol)和4-甲酰基哌啶-1-甲酸叔丁酯(220.6mg,1.03mmol)的混合物搅拌15分钟。在室温下添加$NaBH(OAc)_3$(437mg,2.06mmol)。将反应混合物再搅拌1小

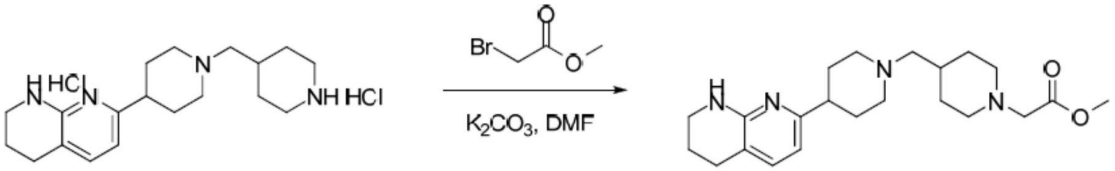
时，用水(10mL)稀释，和用DCM(20mL x 2)萃取。将合并的有机层用水(10mL)和盐水(10mL)洗涤，经Na_2SO_4干燥，过滤和在减压下浓缩。将残余物通过制备型TLC纯化以得到呈无色油的4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-甲酸叔丁酯(148mg，产率:35%)(90%纯度，UV=214nm，ESI 415.1$(M+H)^+$)。

[0293] 步骤5:7-(1-(哌啶-4-基甲基)哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶二盐酸盐

[0294] 

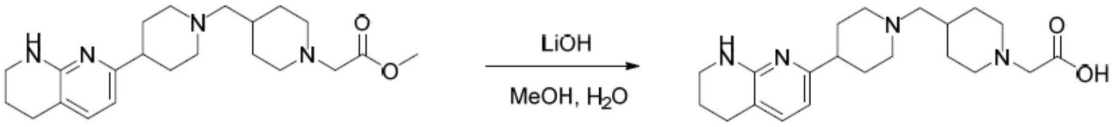
[0295] 在室温下，将4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-甲酸叔丁酯(148mg，0.36mmol)用HCl的1,4-二噁烷溶液(4N，2mL)处理2小时。于真空中去除溶剂以得到呈白色固体的粗制7-(1-(哌啶-4-基甲基)哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶二盐酸盐(135mg粗物质)。产率95%(ESI 315.2$(M+H)^+$)。将粗产物直接用于下个步骤。

[0296] 步骤6:2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-基)乙酸甲酯

[0297] 

[0298] 将含于无水DMF(5mL)中的7-(1-(哌啶-4-基甲基)哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶二盐酸盐(135mg粗物质)、2-溴乙酸甲酯(64mg，0.42mmol)和K_2CO_3(138mg，1.0mmol)的混合物在室温下搅拌5小时。将反应过滤和于真空中浓缩。将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-基)乙酸甲酯(54mg，52%产率)。(91%纯度，UV=254nm，ESI 387.2$(M+H)^+$)。

[0299] 步骤7:2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-基)乙酸(化合物1)

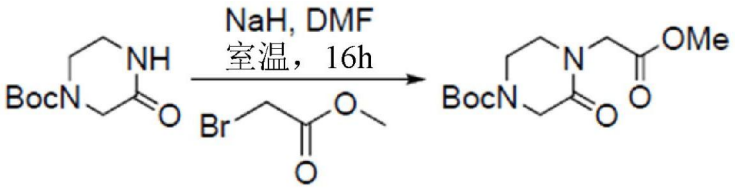
[0300] 

[0301] 在室温下，将2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-基)乙酸甲酯(54mg，0.14mmol)用含于MeOH(3mL)和H_2O(1mL)中的LiOH(21mg，0.5mmol)处理2小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的化合物1(15mg，29%产率)。LC/MS D:100%纯度，UV=214nm，Rt=0.38min，ESI 373.3$(M+H)^+$。^{1}H NMR(500MHz，MeOD)δ7.43(d，J=7.4Hz，1H)，6.55(d，J=7.4Hz，1H)，3.75-3.61(m，4H)，3.53(d，J=11.9Hz，2H)，3.49-3.42(m，2H)，3.06(t，J=11.8Hz，2H)，2.92(d，J=6.5Hz，2H)，2.85(s，3H)，2.79(t，J=6.2Hz，2H)，2.08-2.01(m，7H)，1.98-1.90(m，2H)，1.68(d，J=12.2Hz，2H)。

[0302] 实例2:制备2-(2-氧代基-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-

羰基)哌嗪-1-基)乙酸(化合物2)

[0303] 步骤1:4-(2-甲氧基-2-氧代基乙基)-3-氧代基哌嗪-1-甲酸叔丁酯

[0304] 

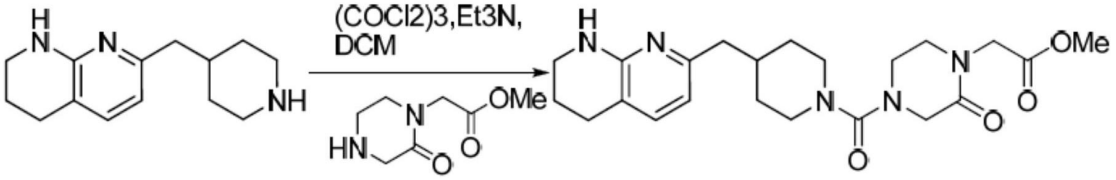
[0305] 在0℃下,向含于DMF(50mL)中的3-氧代基哌嗪-1-甲酸叔丁酯(5.00g,25.0mmol)的溶液中添加NaH(60%含于矿物油中,1.20g,30.0mmol)。将混合物搅拌30分钟,和然后添加2-溴乙酸甲酯(2.60mL,27.5mmol)。将反应在室温下搅拌16小时,然后用H_2O(50mL)中止和用EtOAc(50mLx3)萃取。将合并的有机萃取物用盐水洗涤,经Na_2SO_4干燥,过滤和于真空中浓缩。将残余物通过硅胶柱(石油醚:EtOAc 5:1至2:1)纯化以得到呈无色油的所需化合物(4.0g)。产率59%(86%纯度,UV=214nm,ESI 217.0(M+H)+)。

[0306] 步骤2:2-(2-氧代基哌嗪-1-基)乙酸甲酯

[0307] 

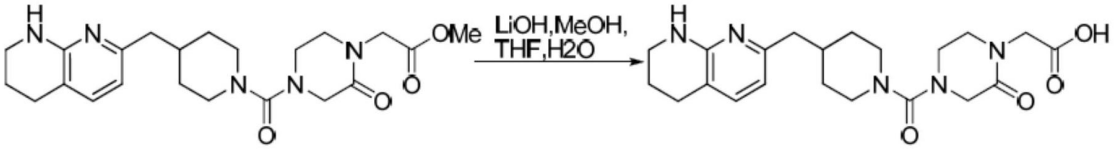
[0308] 在室温下,将4-(2-甲氧基-2-氧代基乙基)-3-氧代基哌嗪-1-甲酸叔丁酯(2.50g,9.18mmol)用HCl/EtOAc的溶液(4.0M,20mL)处理2小时。于真空中去除溶剂以得到呈灰白色固体的所需产物2-(2-氧代基哌嗪-1-基)乙酸甲酯(1.50g)。产率98%(88%纯度,UV=214nm,ESI 173.1(M+H)+)。

[0309] 步骤3:2-(2-氧代基-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)哌嗪-1-基)乙酸甲酯

[0310] 

[0311] 在0℃下,向含于DCM(10mL)中的7-(哌啶-4-基甲基)-1,2,3,4-四氢-1,8-萘啶(200mg,0.75mmol)和三乙胺(300mg,2.96mmol)的混合物中添加三光气(111mg,0.37mmol)。将混合物搅拌30分钟,和然后添加含于DCM(5.0mL)中的2-(2-氧代基哌嗪-1-基)乙酸甲酯(187mg,0.90mmol)。将混合物在室温下搅拌16小时。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈灰白色固体的所需产物(300mg)。产率93%(81%纯度,UV=214nm,ESI 430.3(M+H)+)。

[0312] 步骤4:2-(2-氧代基-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)哌嗪-1-基)乙酸(化合物2)

[0313] 

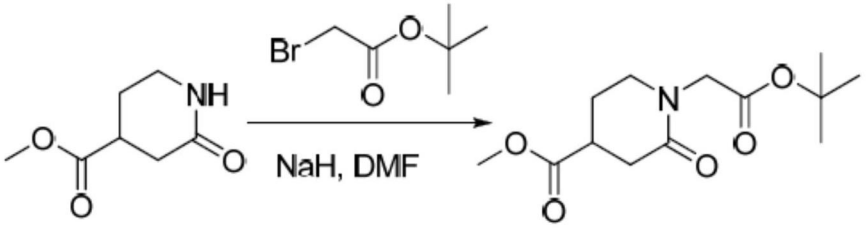
[0314] 在室温下,将2-(2-氧代基-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-

羰基)哌嗪-1-基)乙酸甲酯(300mg,0.70mmol)用含于THF/MeOH/水(5mL/5mL/5mL)中的LiOH-H_2O(117mg,2.79mmol)处理16小时。于真空中去除溶剂,和将残余物通过制备型-HPLC B(30至55%MeCN)纯化以得到呈白色固体的化合物2(88mg),产率23%。LC/MS D:100%纯度,UV=214nm,Rt=0.939min,ESI 416.1(M+H)+)。^{1}H NMR(400MHz,DMSO-d6)δ8.15(0.25H,HCOOH),7.05(d,J=7.2Hz,1H),6.55(s,1H),6.24(d,J=7.2Hz,1H),4.00(s,2H),3.78(s,2H),3.58-3.54(m,2H),3.39-3.38(m,4H),3.24(s,2H),2.71-2.65(m,2H),2.62-2.59(m,2H),2.37-2.39(m,2H),1.80-1.73(m,3H),1.56-1.53(m,2H),1.15-1.06(m,2H)。

[0315] 实例3:制备2-(2-氧代基-4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)哌啶-1-基)乙酸(化合物3)

[0316] 步骤1:1-(2-叔丁氧基-2-氧代基乙基)-2-氧代基哌啶-4-甲酸甲酯

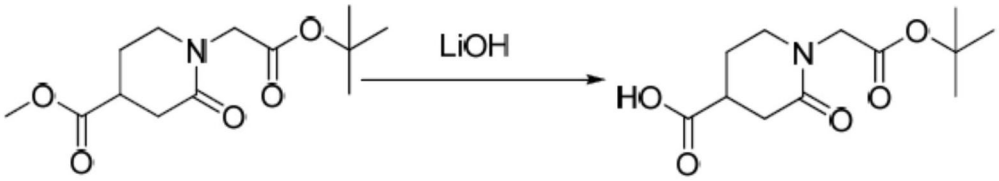
[0317]



[0318] 在0℃下,向含于DMF(30mL)中的2-氧代基哌啶-4-甲酸甲酯(2.90g,18.4mmol)的溶液中添加NaH(60%含于矿物油中,886mg,22.1mmol)。将混合物搅拌30分钟,和然后添加2-溴乙酸叔丁酯(4.32g,22.1mmol)。将反应在室温下搅拌16小时,然后用水(20mL)中止,和用EtOAc(50mLx5)萃取。将合并的有机萃取物用盐水洗涤,经Na_2SO_4干燥,过滤和于真空中浓缩。将残余物通过硅胶柱(石油醚:EtOAc 4:1)纯化以得到呈无色油的1-(2-叔丁氧基-2-氧代基乙基)-2-氧代基哌啶-4-甲酸甲酯(1.5g)。产率30%(90%纯度,UV=214nm,ESI216.1(M+H)+)。

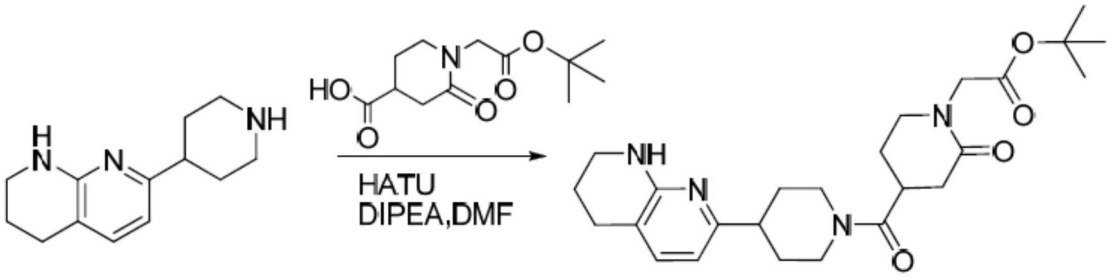
[0319] 步骤2:1-(2-叔丁氧基-2-氧代基乙基)-2-氧代基哌啶-4-甲酸

[0320]



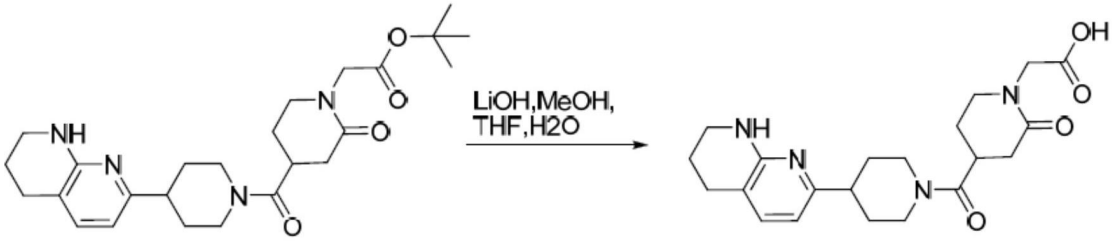
[0321] 在室温下,将1-(2-叔丁氧基-2-氧代基乙基)-2-氧代基哌啶-4-甲酸甲酯(1.00g,3.68mmol)用含于THF/MeOH/水(20mL/20mL/20mL)中的LiOH-H_2O(201mg,4.79mmol)处理16小时。将混合物用HCl水溶液(3.0M,10mL)调整至pH～5和用EtOAc(50mL x 3)萃取。将合并的有机萃取物用盐水洗涤,经Na_2SO_4干燥,过滤和于真空中浓缩以得到呈浅黄色油的所需产物1-(2-叔丁氧基-2-氧代基乙基)-2-氧代基哌啶-4-甲酸(900mg)。产率95%(85%纯度,UV=214nm,ESI 202.0(M+H)+)。

[0322] 步骤3:2-(2-氧代基-4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)哌啶-1-基)乙酸叔丁酯

[0323] 

[0324] 在50℃下，将含于DMF(5.0mL)中的1-(2-叔丁氧基-2-氧代基乙基)-2-氧代基哌啶-4-甲酸(150mg，0.58mmol)和7-(哌啶-4-基)-1,2,3,4-四氢-1,8-萘啶(178mg，0.70mmol)、DIEA(500mg，3.87mmol)和HATU(450mg，1.18mmol)的混合物搅拌2小时。将混合物于真空中浓缩，和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈浅黄色油的所需产物(150mg)。产率56%(86%纯度，UV＝214nm，ESI 457.4(M+H)+)。

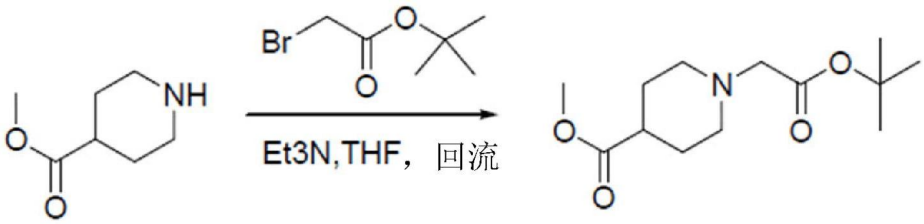
[0325] 步骤4：2-(2-氧代基-4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)哌啶-1-基)乙酸(化合物3)

[0326] 

[0327] 在室温下，将2-(2-氧代基-4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)哌啶-1-基)乙酸叔丁酯(150mg，0.33mmol)用含于THF/MeOH/水(5mL/5mL/5mL)中的LiOH-H_2O(69mg，1.64mmol)处理16小时。于真空中去除溶剂，和将残余物通过制备型-HPLC B(33至50%MeCN)纯化以得到呈白色固体的所需产物化合物3(20mg，15%产率)。LC/MS D:96%纯度，UV＝214nm，Rt＝1.373min，ESI 401.1(M+H)+。^{1}H NMR(400MHz，DMSO-d6)δ8.14(0.15H，HCOOH)，7.10(d，J＝7.2Hz，1H)，6.38-6.36(m，1H)，6.31(d，J＝7.2Hz，1H)，4.51-4.48(m，1H)，4.11-4.04(m，2H)，3.87-3.83(m，1H)，3.43-3.40(m，2H)，3.29-3.24(m，5H)，3.13-3.06(m，1H)，2.69-2.57(m，4H)，2.40-2.26(m，2H)，1.91-1.88(m，1H)，1.78-1.73(m，5H)，1.61-1.55(m，1H)，1.47-1.44(m，1H)。

[0328] 实例4：制备2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸(化合物4)

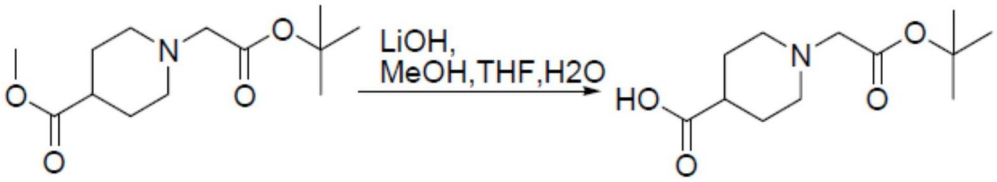
[0329] 步骤1：1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸甲酯

[0330] 

[0331] 向含于THF(20mL)中的哌啶-4-甲酸甲酯(1.43g，1mmol)和三乙胺(2.02g，2mmol)的溶液中添加溴-乙酸叔丁酯(1.95g，1mmol)。将所得混合物在回流下加热过夜。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 1:1)纯化以得到呈无色油的所需产物1-

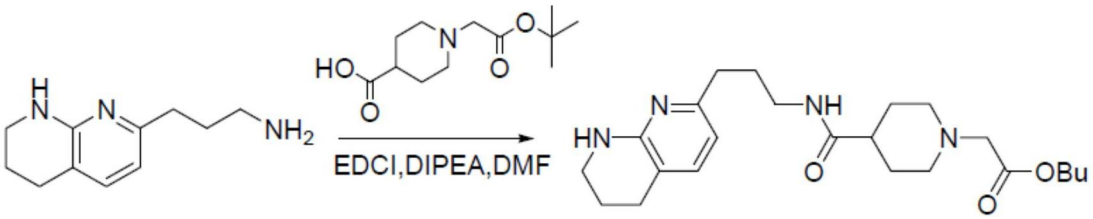
(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸甲酯(0.77g)。产率30%。^{1}H NMR(400MHz,CDCl3) δ3.68(s,3H),3.11(s,2H),2.95-2.87(m,2H),2.33-2.21(m,3H),1.94-1.77(m,4H),1.46(s,9H)。

[0332] 步骤2:1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸

[0333] 

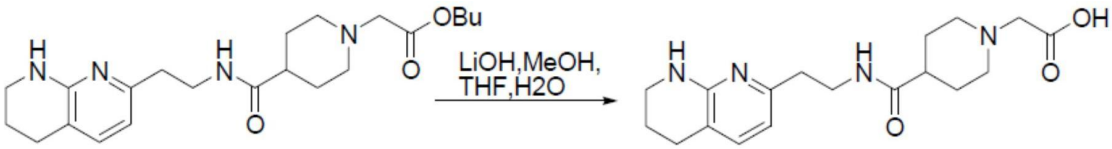
[0334] 在室温下,将1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸甲酯(0.77g,3.0mmol)的混合物用含于MeOH(10mL)、THF(5mL)和H_2O(5mL)中的LiOH-H_2O(126mg,3.0mmol)处理过夜。于真空中去除有机溶剂;然后添加HCl水溶液(1N)至pH～5。将混合物用EtOAc(10mL x 3)萃取。将合并的有机层用盐水洗涤,经无水硫酸钠干燥,过滤和于真空中浓缩以得到呈无色油的所需产物1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸(590mg)。产率81%(ESI 244(M+H)+)。

[0335] 步骤3:2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸丁酯

[0336] 

[0337] 在50℃下,将含于DMF(4mL)中的3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙-1-胺盐酸盐(140mg,0.62mmol)、1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸(100mg,0.41mmol)、EDCI(118mg,0.62mmol)和DIPEA(159mg,1.23mmol)的混合物搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈黄色油的所需产物2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸丁酯(120mg)。产率70%(95%纯度,UV=254nm,ESI 417.2(M+H)+)。

[0338] 步骤4:2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸(化合物4)

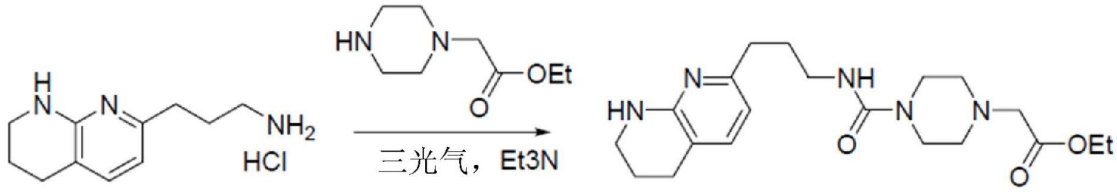
[0339] 

[0340] 在40℃下,将2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸丁酯(120mg,0.29mmol)用含于MeOH(4mL)、THF(2mL)和H_2O(2mL)中的LiOH-H_2O(59mg,1.40mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物4(40mg,39%产率)。LC/MS C:100%纯度,UV=214nm,Rt=1.36min,ESI 361(M+H)+。^{1}H NMR(500MHz,CD_3OD)δ7.16(d,J=7.0Hz,1H),6.39(d,J=7.0Hz,1H),3.66-3.55(m,4H),3.39(t,J=5.5Hz,2H),3.22(t,J=7.0Hz,2H),3.04-

2.96(m,2H),2.72(t,J=6.5Hz,2H),2.58-2.43(m,3H),2.05-1.98(m,4H),1.92-1.80(m,4H)。

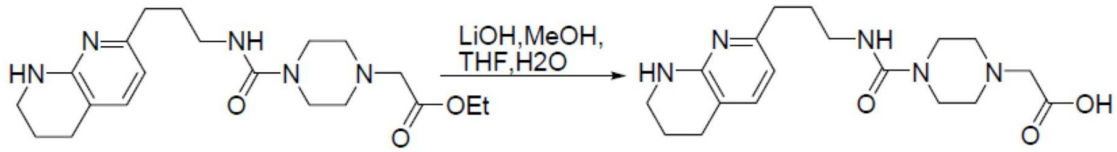
[0341] 实例5:制备2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸(化合物5)

[0342] 步骤1:2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸乙酯

[0343] 

[0344] 在0℃下,向含于DCM(6mL)中的3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙-1-胺盐酸盐(200mg,0.88mmol)和三乙胺(177mg,1.75mmol)的混合物中添加三光气(157mg,0.52mmol)。将混合物搅拌30分钟,和然后添加含于DCM(2mL)中的2-(哌嗪-1-基)乙酸乙酯(151mg,0.88mmol)。将混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 10:1)纯化以得到呈白色固体的所需产物(226mg)。产率66%(ESI 390.1(M+H)+)。

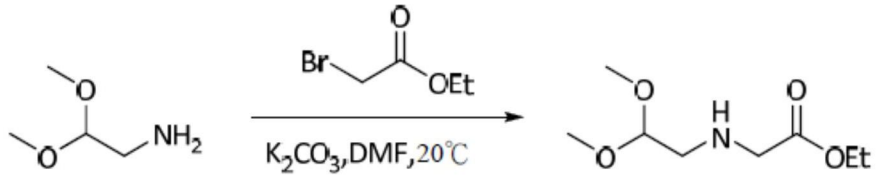
[0345] 步骤2:2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸(化合物5)

[0346] 

[0347] 在室温下,将2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸乙酯(200mg,0.51mmol)用含于MeOH(4mL)、THF(2mL)和H_2O(2mL)中的LiOH-H_2O(100mg,2.38mmol)处理过夜。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物5(MRT-A0034)(45mg),产率24%。LC/MS B:100%纯度,UV=214nm,Rt=0.794min,ESI 362.1(M+H)+)。^{1}H NMR(400MHz,CD_3OD)δ7.18(d,J=7.2Hz,1H),6.41(d,J=7.2Hz,1H),3.48-3.41(m,4H),3.39(t,J=5.6Hz,2H),3.19(t,J=6.8Hz,2H),3.12(s,2H),2.75-2.65(m,6H),2.56(t,J=7.6Hz,2H),1.91-1.80(m,4H)。

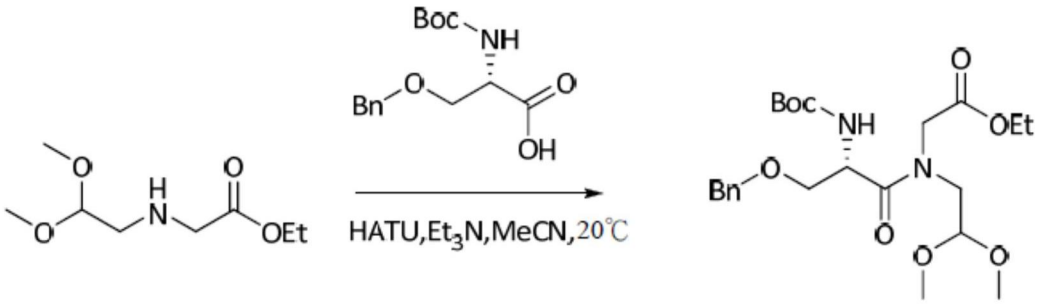
[0348] 实例6:制备(S)-2-(3-(羟甲基)-2-氧代基-4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸(化合物6)

[0349] 步骤1:2-(2,2-二甲氧基乙氨基)乙酸乙酯

[0350] 

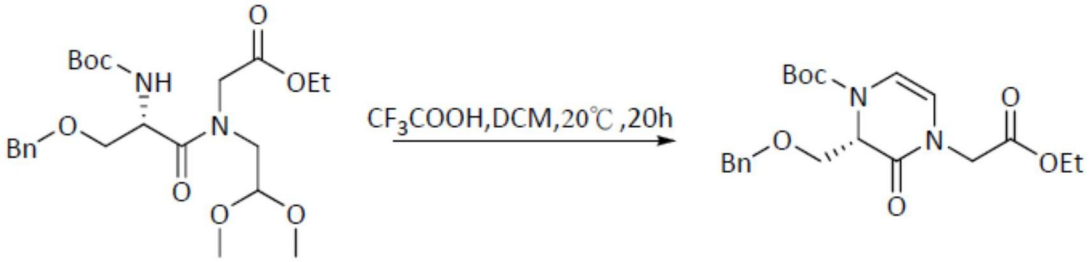
[0351] 将含于DMF(40mL)中的2,2-二甲氧基乙胺(5.0g,47.55mmol)、2-溴乙酸乙酯(7.9g,47.30mmol)和K_2CO_3(6.64g,48.04mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈无色油的所需产物2-(2,2-二甲氧基乙氨基)乙酸乙酯(6.5g)。产率71%(ESI191.0$(M+H)^+$)。

[0352] 步骤2：(S)-2-(3-(苄氧基)-2-(叔丁氧基羰基氨基)-N-(2,2-二甲氧基乙基)丙酰氨基)乙酸乙酯

[0353] 

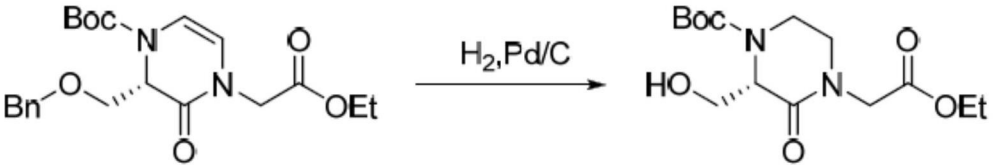
[0354] 将含于MeCN(10mL)中的2-(2,2-二甲氧基乙氨基)乙酸乙酯(1.0g,5.23mmol)、(S)-3-(苄氧基)-2-(叔丁氧羰基氨基)丙酸(1.54g,5.23mmol)、HATU(2.98g,7.84mmol)和DIEA(2.02g,15.68mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 1:1)纯化以得到呈无色油的所需产物(S)-2-(3-(苄氧基)-2-(叔丁氧基羰基氨基)-N-(2,2-二甲氧基乙基)丙酰氨基)乙酸乙酯(1.9g)。产率77%(ESI 468(M+H)$^+$)。

[0355] 步骤3：(S)-2-(苄氧基甲基)-4-(2-乙氧基-2-氧代基乙基)-3-氧代基-3,4-二氢吡嗪-1(2H)-甲酸叔丁酯

[0356] 

[0357] 将含于DCM(10mL)中的(S)-2-(3-(苄氧基)-2-(叔丁氧基羰基氨基)-N-(2,2-二甲氧基乙基)丙酰氨基)乙酸乙酯(1.5g,3.2mmol)和CF_3COOH(1.09g,9.6mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 1:1)纯化以得到呈无色油的所需产物(S)-2-(苄氧基甲基)-4-(2-乙氧基-2-氧代基乙基)-3-氧代基-3,4-二氢吡嗪-1(2H)-甲酸叔丁酯(700mg)。产率72%(ESI 404(M+H)+)。^{1}H NMR(500MHz,CD_3OD)δ7.20(d,J＝3.8Hz,6H),6.36-6.13(m,1H),5.63(dd,J＝49.5,6.0Hz,1H),4.92-4.81(m,1H),4.51-4.33(m,3H),4.17(d,J＝4.8Hz,2H),4.12-4.02(m,2H),3.72-3.62(m,1H),3.57-3.46(m,1H),1.41-1.32(m,10H),1.15(t,J＝7.1Hz,4H)。

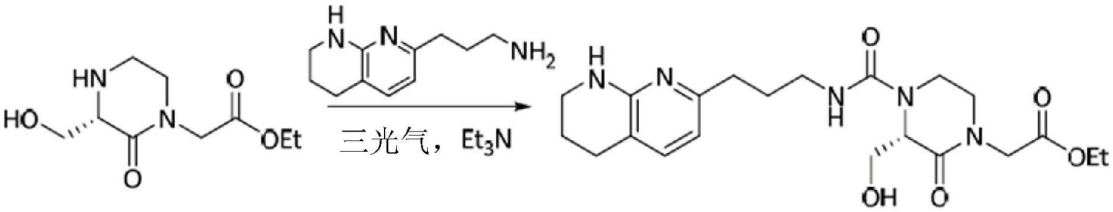
[0358] 步骤4：(S)-4-(2-乙氧基-2-氧代基乙基)-2-(羟甲基)-3-氧代基哌嗪-1-甲酸叔丁酯

[0359] 

[0360] 在H_2气球下，在室温下，将含于MeOH(10mL)中的(S)-2-(苄氧基甲基)-4-(2-乙氧基-2-氧代基乙基)-3-氧代基-3,4-二氢吡嗪-1(2H)-甲酸叔丁酯(700mg,2.3mmol)和Pd/C

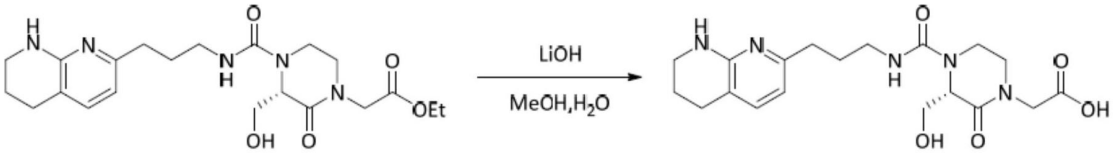
(140mg,20重量%)的混合物搅拌过夜。将悬浮液通过硅藻土垫过滤和将滤饼用MeOH(10mL×2)洗涤。将合并的滤液于真空中浓缩,和将残余物通过硅胶柱(石油醚:EtOAc 1:1)纯化以得到呈无色油的所需产物(S)-4-(2-乙氧基-2-氧代基乙基)-2-(羟甲基)-3-氧代基哌嗪-1-甲酸叔丁酯(540mg)。产率99%(ESI 316(M+H)+)。

[0361] 步骤5:(S)-2-(3-(羟甲基)-2-氧代基-4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸乙酯

[0362] 

[0363] 在0℃下,将含于DCM(8mL)中的3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙-1-胺(212mg,1.11mmol)、三光气(137mg,0.46mmol)和三乙胺(562mg,5.55mmol)的混合物搅拌1小时。在0℃下,通过注射器逐滴添加含于DCM(2mL)中的(S)-4-(2-乙氧基-2-氧代基乙基)-2-(羟甲基)-3-氧代基哌嗪-1-甲酸叔丁酯(200mg,0.93mmol)的溶液。将反应混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:CH_3OH 20:1)纯化以得到呈无色油的所需产物(S)-2-(3-(羟甲基)-2-氧代基-4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸乙酯(250mg)。产率63%(ESI 433$(M+H)^+$)。

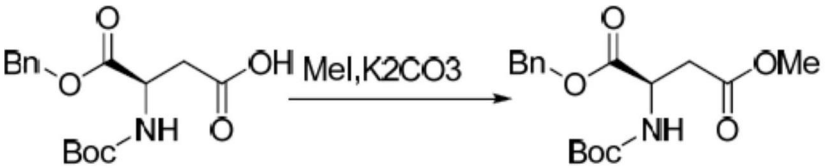
[0364] 步骤6:(S)-2-(3-(羟甲基)-2-氧代基-4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸(化合物6)

[0365] 

[0366] 在室温下,将(S)-2-(3-(羟甲基)-2-氧代基-4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌嗪-1-基)乙酸乙酯(250mg,0.58mmol)用含于MeOH(4mL)和H_2O(1mL)中的LiOH-H_2O(97mg,2.31mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物6(25mg,11%产率)。LC/MS B:100%纯度,UV=214nm,Rt=0.58min,ESI 405.5(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.49(d,J=7.3Hz,1H),6.55(d,J=7.4Hz,1H),4.59(d,J=16.6Hz,2H),4.09(dd,J=11.5,7.1Hz,2H),3.92(dd,J=11.6,3.5Hz,1H),3.78(dd,J=11.7,4.1Hz,1H),3.68(d,J=11.6Hz,1H),3.49-3.35(m,4H),3.20(d,J=8.1Hz,2H),2.80-2.60(m,4H),1.97-1.70(m,4H)。

[0367] 实例7:制备2-(3-(1-甲基-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)脲基)-2-氧代基吡咯烷-1-基)乙酸(化合物7-E1和7-E2)

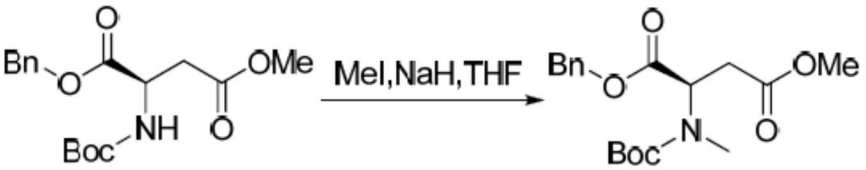
[0368] 步骤1:(R)-2-(叔丁氧羰基氨基)琥珀酸1-苄酯4-甲酯

[0369] 

[0370] 将含于丙酮(500mL)中的(R)-4-(苄氧基)-3-(叔丁氧羰基氨基)-4-氧代基丁酸

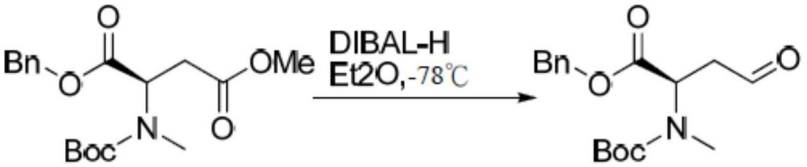
(11.0g,34.0mmol)、K_2CO_3(17.0g,123mmol)和MeI(6.50mL,104mmol)的混合物在室温下搅拌16小时。将混合物浓缩,用水稀释和用EtOAc(200mL x 5)萃取。将合并的有机萃取物用盐水洗涤和经Na_2SO_4干燥,过滤和于真空中浓缩以得到呈黄色固体的(R)-2-(叔丁氧羰基氨基)琥珀酸1-苄酯4-甲酯(11.0g)。产率98%(94%纯度,UV=214nm,ESI 238.1(M+H)+)。

[0371] 步骤2:(R)-2-(叔丁氧羰基(甲基)氨基)琥珀酸1-苄酯4-甲酯

[0372] 

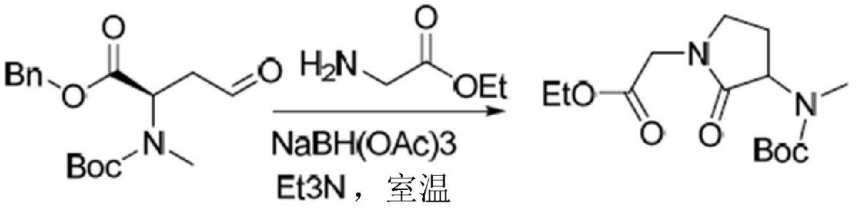
[0373] 在0℃下,向含于DMF(30mL)中的(R)-2-(叔丁氧羰基氨基)琥珀酸1-苄酯4-甲酯(3.00g,8.89mmol)和MeI(1.50mL,24.1mmol)的溶液中添加NaH(60%含于矿物油中,533mg,13.3mmol)。将混合物在室温下搅拌1小时,然后用水(20mL)稀释和用EtOAc(50mL x 5)萃取。将合并的有机萃取物用盐水洗涤和经Na_2SO_4干燥,过滤和于真空中浓缩以得到呈黄色油的(R)-2-(叔丁氧羰基(甲基)氨基)琥珀酸1-苄酯4-甲酯(3.00g)。产率98%(88%纯度,UV=214nm,ESI252.3(M+H)+)。

[0374] 步骤3:(R)-2-(叔丁氧羰基(甲基)氨基)-4-氧代基丁酸苄酯

[0375] 

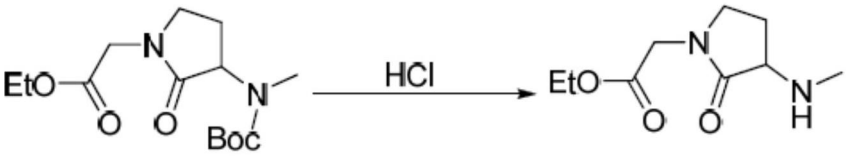
[0376] 在-78℃下,向含于无水Et_2O(150mL)中的(R)-2-(叔丁氧羰基(甲基)氨基)琥珀酸1-苄酯4-甲酯(3.00g,8.54mmol)的溶液中逐滴添加DIBAL-H(1.0M,17.0mL)。将混合物在-78℃下搅拌1小时,然后用饱和NH_4Cl水溶液(20mL)中止。将混合物在室温下搅拌1小时,然后过滤和用EtOAc(50mL x 3)萃取。将合并的有机萃取物用盐水洗涤,经Na_2SO_4干燥,过滤和于真空中浓缩以得到呈浅黄色油的所需产物(2.5g)。产率92%(80%纯度,UV=214nm,ESI 222.4(M+H)+)。

[0377] 步骤4:2-(3-(叔丁氧羰基(甲基)氨基)-2-氧代基吡咯烷-1-基)乙酸乙酯

[0378] 

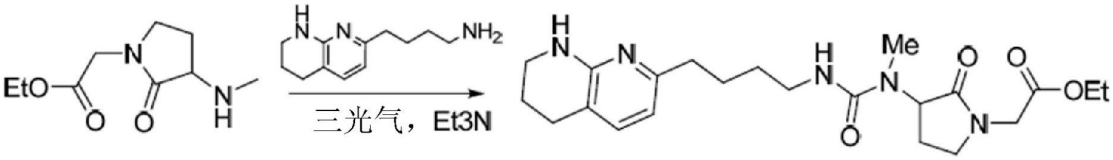
[0379] 将含于DCM(100mL)中的2-氨基乙酸乙酯(4.42g,31.7mmol)、三乙胺(7.5mL,54.1mmol)、$NaBH(OAc)_3$(4.00g,18.8mmol)、乙酸(催化量(cat))和(R)-2-(叔丁氧羰基(甲基)氨基)-4-氧代基丁酸苄酯(1.61g,5.01mmol)的混合物在室温下搅拌16小时。将反应用水(20mL)中止和用DCM(50mL x 3)萃取。将合并的有机萃取物于真空中浓缩,和将残余物通过逆相C18柱(35%至50%MeCN/H_2O(0.5%NH_4HCO_3))纯化以得到呈浅黄色油的所需产物(410mg)。产率18%(95%纯度,UV=214nm,ESI 201.3(M+H)+)。

[0380] 步骤5:2-(3-(甲氨基)-2-氧代基吡咯烷-1-基)乙酸乙酯

[0381] 

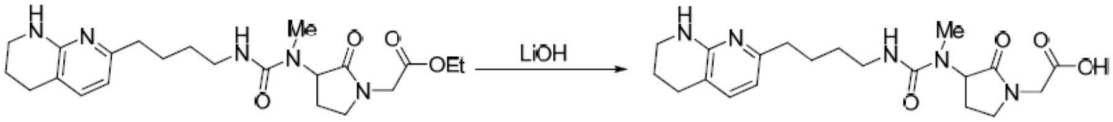
[0382] 在室温下，将2-(3-(叔丁氧羰基(甲基)氨基)-2-氧代基吡咯烷-1-基)乙酸乙酯(410mg，1.36mmol)用HCl的二噁烷溶液(4.0M，10mL)处理2小时。将反应于真空中浓缩以得到呈浅黄色固体的所需产物(340mg)。产率95%(95%纯度，UV＝214nm，ESI 201.3(M+H)+)。

[0383] 步骤6：2-(3-(1-甲基-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)脲基)-2-氧代基吡咯烷-1-基)乙酸乙酯

[0384] 

[0385] 在0℃下，向含于DCM(20mL)中的4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁-1-胺(375mg，1.55mmol)和三乙胺(1.00mL)的混合物中添加三光气(250mg，0.85mmol)。将混合物搅拌30分钟，和然后添加含于DCM(5mL)中的2-(3-(甲氨基)-2-氧代基吡咯烷-1-基)乙酸乙酯(340mg，1.68mmol)。将混合物在室温下搅拌16小时。于真空中去除溶剂，和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈浅黄色固体的所需产物2-(3-(1-甲基-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)脲基)-2-氧代基吡咯烷-1-基)乙酸乙酯(300mg)。产率45%(82%纯度，UV＝214nm，ESI 432.4(M+H)+)。

[0386] 步骤7：2-(3-(1-甲基-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)脲基)-2-氧代基吡咯烷-1-基)乙酸(化合物7-E1和7-E2)

[0387] 

[0388] 在室温下，将2-(3-(1-甲基-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)脲基)-2-氧代基吡咯烷-1-基)乙酸乙酯(300mg，0.70mmol)用含于MeOH(7.5mL)和水(2.5mL)中的LiOH-H_2O(292mg，6.95mmol)处理2小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(35至65%MeCN)纯化以得到呈白色固体的外消旋化合物7(245mg，85%产率)。将所述外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物7-E1(118mg)和化合物7-E2(95mg)。

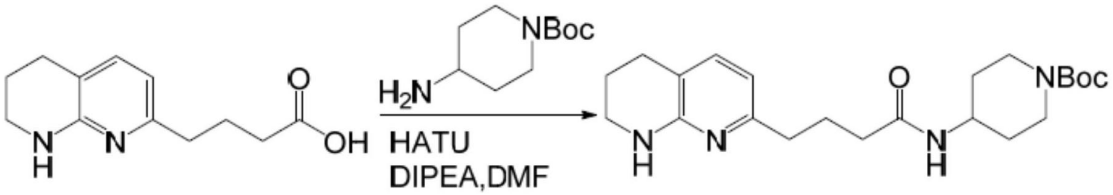
[0389] 化合物7-E1 LC/MS A：96%纯度，UV＝214nm，Rt＝1.376min，ESI404.3(M+H)+。^{1}H NMR(400MHz，D_2O)δ7.02(d，J＝6.8Hz，1H)，6.38(m，2)，6.25(d，J＝7.2Hz，1H)，4.90(m，1H)，3.94-3.81(m，2H)，3.22(m，4H)，3.02-2.97(m，2H)，2.60(m，4H)，2.43-2.40(m，3H)，2.14-2.08(m，1H)，1.89-1.84(m，1H)，1.75-1.71(m，2H)，1.56-1.53(m，2H)，1.41-1.40(m，2H)。手性SFC A(40%MeOH)：ee 100%，Rt＝1.91min。

[0390] 化合物7-E2 LC/MS A：99.5%纯度，UV＝214nm，Rt＝1.37min，ESI404.4(M+H)+。^{1}H NMR(400MHz，CD_3OD)δ7.02(d，J＝6.8Hz，1H)，6.38(m，2)，6.25(d，J＝7.2Hz，1H)，4.90(m，1H)，3.94-3.81(m，2H)，3.22(m，4H)，3.02-2.97(m，2H)，2.60(m，4H)，2.43-2.40(m，3H)，2.14-2.08(m，1H)，1.89-1.84(m，1H)，1.75-1.71(m，2H)，1.56-1.53(m，2H)，1.41-1.40(m，

2H)。手性SFC A(40%MeOH):ee 100%,Rt=4.02min。

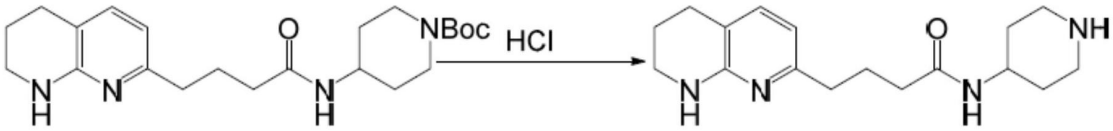
[0391] 实例8:制备2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸(化合物8-E1和8-E2)

[0392] 步骤1:4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-甲酸叔丁酯

[0393] 

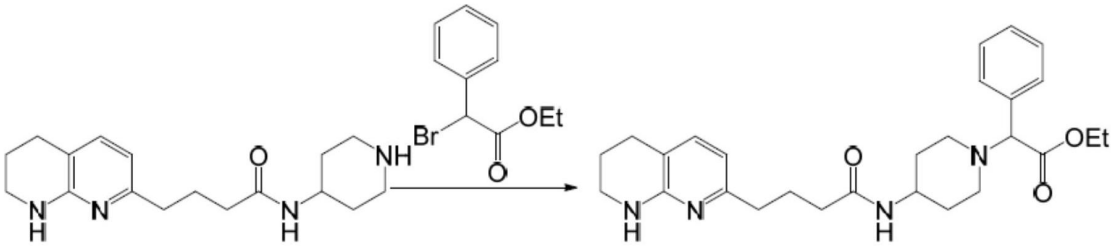
[0394] 将含于DMF(6mL)中的4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酸(500mg,2.27mmol)、4-氨基哌啶-1-甲酸叔丁酯(454mg,2.27mmol)、HATU(1296mg,3.41mmol)和DIEA(879mg,6.81mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈黄色油的所需产物4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-甲酸叔丁酯(620mg)。产率68%(98%纯度,UV=214nm,ESI 402.0$(M+H)^+$)。

[0395] 步骤2:N-(哌啶-4-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺

[0396] 

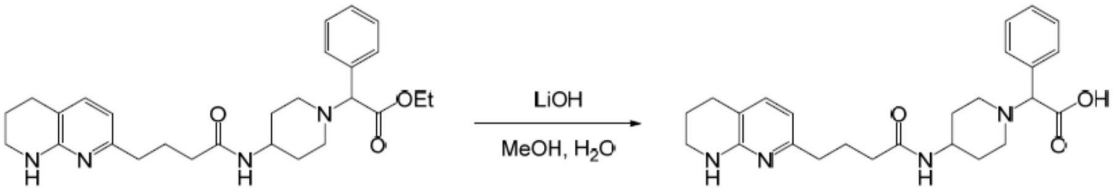
[0397] 在室温下,将4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-甲酸叔丁酯(620mg,1.54mmol)用含于1,4-二噁烷(5mL)中的HCl(4mL,15.4mmol)处理过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 40:1)纯化以得到呈黄色油的所需产物N-(哌啶-4-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺(440mg)。产率95%(100%纯度,UV=214nm,ESI 302$(M+H)^+$)。

[0398] 步骤3:2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸乙酯

[0399] 

[0400] 在50℃下,将含于MeCN(4mL)中的N-(哌啶-4-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺(200mg,0.66mmol)、2-溴-2-苯基乙酸乙酯(192mg,0.79mmol)、DIEA(255mg,1.98mmol)和K_2CO_3(273mg,1.98mmol)的混合物搅拌3小时。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈黄色油的所需产物2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸乙酯(160mg)。产率52%(100%纯度,UV=214nm,ESI 464$(M+H)^+$)。

[0401] 步骤4:2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸(化合物8-E1和8-E2)

[0402] 

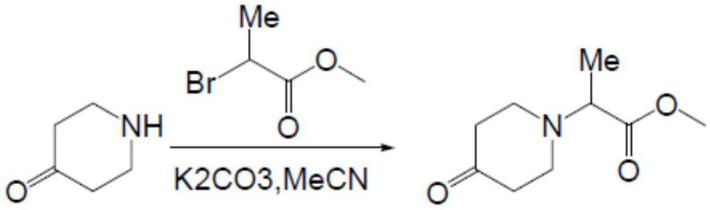
[0403] 在室温下，将2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸乙酯(160mg，0.34mmol)用含于MeOH(4mL)和H_2O(1mL)中的LiOH-H_2O(58mg，1.38mmol)处理2小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的外消旋化合物8(65mg，44%产率)。将所述外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物8-E1(32mg)和化合物8-E2(31mg)。

[0404] 化合物8-E1 LC/MS A:95%纯度，UV＝214nm，Rt＝1.44min，ESI436(M+H)+。^{1}H NMR(400MHz，CD_3OD)δ7.59-7.58(m,2H)，7.42-7.41(m,3H)，7.19(d,J＝7.0Hz,1H)，6.39(d,J＝7.5Hz,1H)，4.33(s,1H)，3.82(m,1H)，3.39-3.32(m,4H)，2.96-2.69(m,6H)，2.56(t,J＝7.5Hz,2H)，2.20(t,J＝7.5Hz,2H)，1.86-1.28(m,6H)。手性SFC A(45%MeOH)：ee 100%，Rt＝2.09min。

[0405] 化合物8-E2 LC/MS A:95.8%纯度，UV＝214nm，Rt＝1.45min，ESI 436(M+H)+。^{1}H NMR(400MHz，CD_3OD)δ7.59-7.58(m,2H)，7.42-7.41(m,3H)，7.19(d,J＝7.0Hz,1H)，6.39(d,J＝7.5Hz,1H)，4.33(s,1H)，3.82(m,1H)，3.39-3.32(m,4H)，2.96-2.69(m,6H)，2.56(t,J＝7.5Hz,2H)，2.20(t,J＝7.5Hz,2H)，1.86-1.28(m,6H)。手性SFC A(45%MeOH)：ee 100%，Rt＝3.8min。

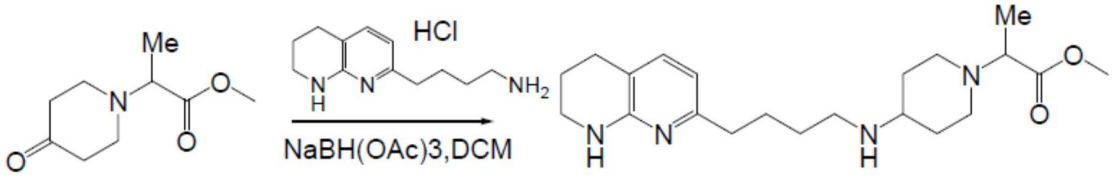
[0406] 实例9：制备2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基氨基)哌啶-1-基)丙酸(化合物9)

[0407] 步骤1：2-(4-氧代基哌啶-1-基)丙酸甲酯

[0408] 

[0409] 将含于MeCN(20mL)中的哌啶-4-酮盐酸盐(1.0g，7.38mmol)、2-溴丙酸甲酯(1.85g，11.06mmol)和K_2CO_3(3.06g，22.13mmol)的混合物在室温下搅拌4小时。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物(1.2g)。产率88%(80%纯度，UV＝214nm，ESI 186.1(M+H)+)。

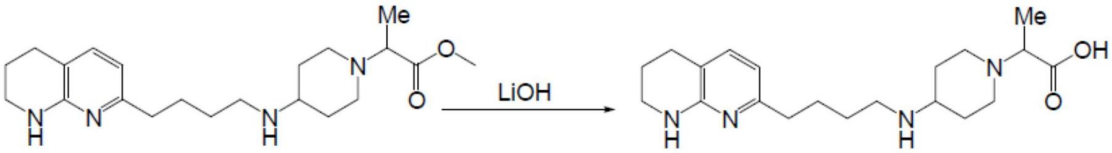
[0410] 步骤2：2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基氨基)哌啶-1-基)丙酸甲酯

[0411] 

[0412] 在室温下，向含于DCM(5mL)中的4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁-1-胺盐酸盐(200mg，0.72mmol)的溶液中添加三乙胺(145mg，1.44mmol)。将混合物搅拌10分钟，和然

后添加2-(4-氧代基哌啶-1-基)丙酸甲酯(213mg,0.86mmol)、$NaBH(OAc)_3$(457mg,2.16mmol)和一滴HOAc。将混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈无色油的所需产物(240mg)。产率89%(100%纯度,UV=254nm,ESI375.3(M+H)+)。

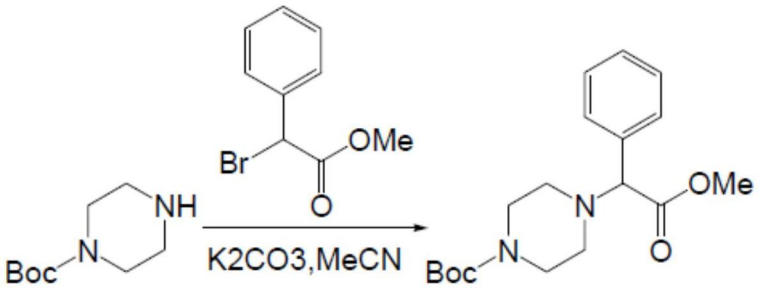
[0413] 步骤3:2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基氨基)哌啶-1-基)丙酸(化合物9)

[0414] 

[0415] 在室温下,将2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基氨基)哌啶-1-基)丙酸甲酯(100mg,0.27mmol)用含于MeOH(4mL)和H_2O(1mL)中的LiOH-H_2O(42mg,1.0mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLCA(30至65%MeCN)纯化以得到化合物9(呈白色固体(35mg,产率36%)。LC/MSC:97.2%纯度,UV=214nm,Rt=1.166min,ESI 361.4(M+H)+)。^{1}H NMR(400MHz,CD_3OD)δ7.14(d,J=7.2Hz,1H),6.38(d,J=7.6Hz,1H),3.39-3.18(m,4H),2.91-2.83(m,3H),2.72-2.53(m,6H),2.15-2.02(m,2H),1.89-1.84(m,2H),1.75-1.59(m,6H),1.36(d,J=6.8Hz,3H)。

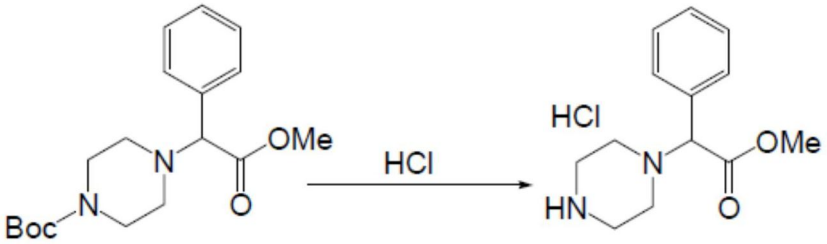
[0416] 实例10:制备2-苯基-2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸(化合物10-E1和10-E2)

[0417] 步骤1:4-(2-甲氧基-2-氧代基-1-苯乙基)哌嗪-1-甲酸叔丁酯

[0418] 

[0419] 将含于MeCN(30mL)中的哌嗪-1-甲酸叔丁酯(1.5g,8.05mmol)、2-溴-2-苯基乙酸甲酯(2.21g,9.66mmol)和K_2CO_3(3.33g,24.15mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 1:2)纯化以得到呈无色油的所需产物(1.6g)。产率60%(ESI 235$(M+H-100)^+$)。

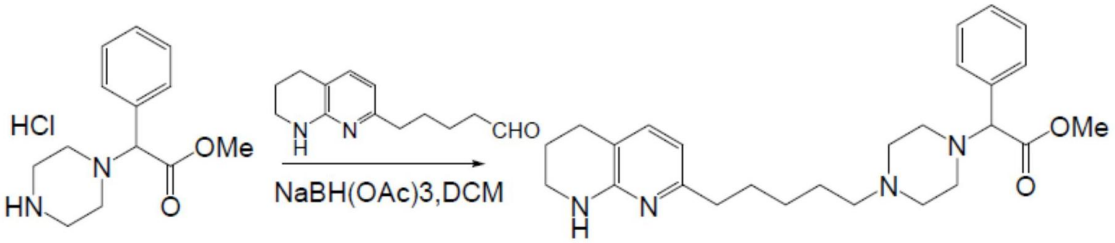
[0420] 步骤2:2-苯基-2-(哌嗪-1-基)乙酸甲酯盐酸盐

[0421] 

[0422] 在室温下,将4-(2-甲氧基-2-氧代基-1-苯乙基)哌嗪-1-甲酸叔丁酯(500mg,1.50mmol)用HCl/二噁烷的溶液(2.0M,10mL)处理2小时,然后于真空中浓缩以得到呈白色

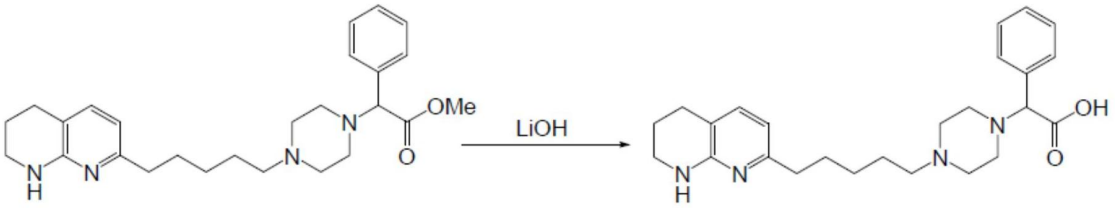
固体的所需产物(389mg)。产率96%(ESI 235(M+H)+)。

[0423] 步骤3:2-苯基-2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸甲酯

[0424] 

[0425] 在室温下,向含于DCM(5mL)中的2-苯基-2-(哌嗪-1-基)乙酸甲酯盐酸盐(150mg,0.55mmol)的溶液中添加三乙胺(112mg,1.11mmol)。将混合物搅拌10分钟,和然后添加5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊醛(120mg,0.55mmol)、$NaBH(OAc)_3$(350mg,1.65mmol)和一滴HOAc。将混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 10:1)纯化以得到呈无色油的所需产物(130mg)。产率54%(100%纯度,UV=254nm,ESI 437.3(M+H)+)。

[0426] 步骤4:2-苯基-2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸(化合物10-E1和10-E2)

[0427] 

[0428] 在室温下,将2-苯基-2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸甲酯(130mg,0.30mmol)用含于MeOH(5.0mL)和H_2O(1.0mL)中的LiOH-H_2O(63mg,1.50mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的外消旋化合物10(70mg,55%产率)。将所述外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物10-E1(21mg)和化合物10-E2(18mg)。

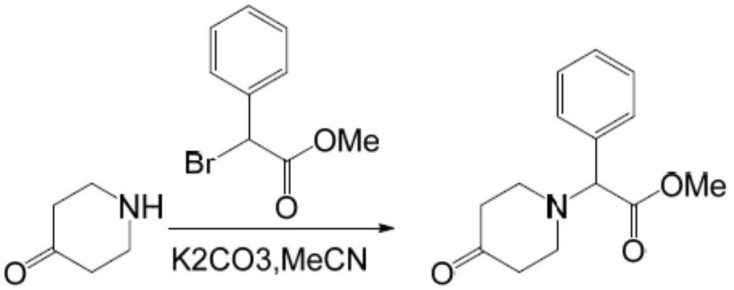
[0429] 化合物10-E1 LC/MS A:95%纯度,UV=214nm,Rt=1.53min,ESI 423.4(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.43-7.41(m,2H),7.24-7.18(m,3H),7.05(d,J=7.6Hz,1H),6.26(d,J=7.2Hz,1H),3.76(s,1H),3.27-3.24(m,2H),2.86-2.39(m,14H),1.80-1.72(m,2H),1.60-1.43(m,4H),1.29-1.17(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=1.93min。

[0430] 化合物10-E2 LC/MS A:95%纯度,UV=214nm,Rt=1.53min,ESI 423.4(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.43-7.41(m,2H),7.24-7.18(m,3H),7.05(d,J=7.6Hz,1H),6.26(d,J=7.2Hz,1H),3.76(s,1H),3.27-3.24(m,2H),2.86-2.39(m,14H),1.80-1.72(m,2H),1.60-1.43(m,4H),1.29-1.17(m,2H)。手性SFC A(45%MeOH):ee 95%,Rt=2.72min。

[0431] 实例11:制备2-苯基-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-基)乙酸(化合物11-E1和11-E2)

[0432] 步骤1:2-(4-氧代基哌啶-1-基)-2-苯基乙酸甲酯

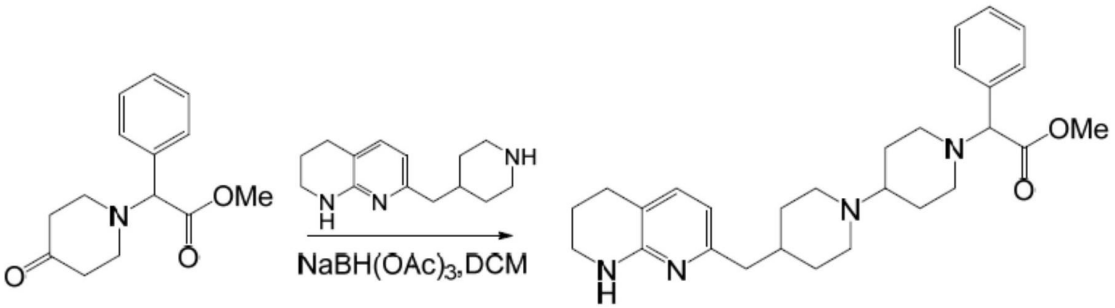
[0433]



[0434] 将含于MeCN(30mL)中的哌啶-4-酮盐酸盐(1.0g,7.38mmol)、2-溴-2-苯基乙酸甲酯(2.53g,11.06mmol)和K_2CO_3(3.06g,22.13mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物2-(4-氧代基哌啶-1-基)-2-苯基乙酸甲酯(1.3g)。产率71%(98%纯度,UV=214nm,ESI 248.0$(M+H)^+$)。

[0435] 步骤2:2-苯基-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-基)乙酸甲酯

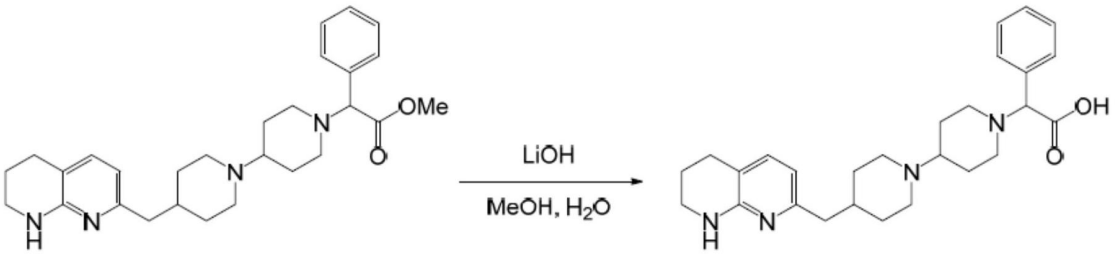
[0436]



[0437] 将含于DCM(5mL)中的7-(哌啶-4-基甲基)-1,2,3,4-四氢-1,8-萘啶(152mg,0.66mmol)、2-(4-氧代基哌啶-1-基)-2-苯基乙酸甲酯(195mg,0.79mmol)和$NaBH(OAc)_3$(418mg,1.97mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈无色油的所需产物2-苯基-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-基)乙酸甲酯(110mg)。产率36%(100%纯度,UV=214nm,ESI 463$(M+H)^+$)。

[0438] 步骤3:2-苯基-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-基)乙酸(化合物11-E1和11-E2)

[0439]



[0440] 在室温下,将2-苯基-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-基)乙酸甲酯(110mg,0.24mmol)用含于MeOH(4mL)和H_2O(1mL)中的LiOH-H_2O(42mg,1.0mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的外消旋化合物11(55mg,52%产率)。将所述外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物11-E1(12mg)和化合物11-E2

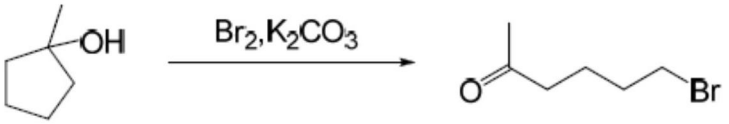
(15mg)。

[0441] 化合物11-E1 LC/MS A:100%纯度,UV=214nm,Rt=1.5min,ESI 449.5(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.54-7.52(m,2H),7.34-7.32(m,3H),7.13(d,J=7.2Hz,1H),6.35(d,J=7.2Hz,1H),3.92(br,1H),3.58-3.20(m,5H),2.90-2.32(m,9H),2.22-1.64(m,10H),1.44-1.25(m,2H)。手性SFC A(40%MeOH):ee 100%,Rt=2.98min。

[0442] 化合物11-E2 LC/MS A:100%纯度,UV=214nm,Rt=1.5min,ESI 449.5(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.54-7.52(m,2H),7.34-7.32(m,3H),7.13(d,J=7.2Hz,1H),6.35(d,J=7.2Hz,1H),3.95(br,1H),3.58-3.20(m,5H),2.90-2.32(m,9H),2.22-1.64(m,10H),1.44-1.25(m,2H)。手性SFC A(40%MeOH):ee 100%,Rt=4.15min。

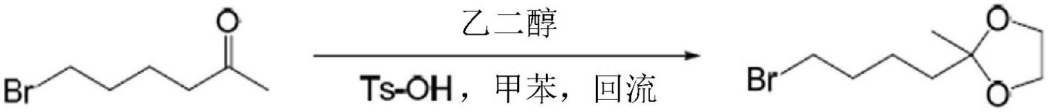
[0443] 实例12:制备2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)哌啶-1-基)乙酸(化合物12-E1和12-E2)

[0444] 步骤1:6-溴己-2-酮

[0445] 

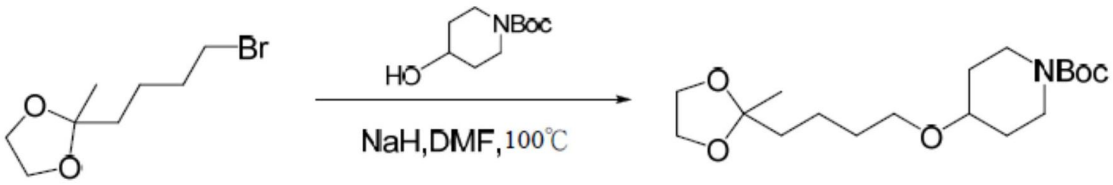
[0446] 在0℃下,将含于$CHCl_3$(130mL)中的1-甲基环戊醇(4.00g,39.94mmol)和K_2CO_3(33.11g,239.6mmol)的混合物搅拌15分钟,和然后添加溴(10.23mL,199.7mmol)。将反应混合物在0℃下搅拌2.5小时,然后缓慢倒入冰冷饱和$Na_2S_2O_3$水溶液(100mL)中。将有机层分离,用水(2x 100mL)洗涤,经$MgSO_4$干燥,过滤和于真空中浓缩。将残余物通过硅胶柱(石油醚:EtOAc 3:1)纯化以得到呈无色油的所需产物6-溴己-2-酮(4g)。产率56%(98%纯度,UV=214nm,ESI未发现)。^{1}H-NMR(400MHz,$CDCl_3$)δ1.66-1.80(m,2H),1.82-1.93(m,2H),2.15(s,3H),2.48(t,J=7.3Hz,2H),3.41(t,J=6.5Hz,2H)。

[0447] 步骤2:2-(4-溴丁基)-2-甲基-1,3-二氧戊环

[0448] 

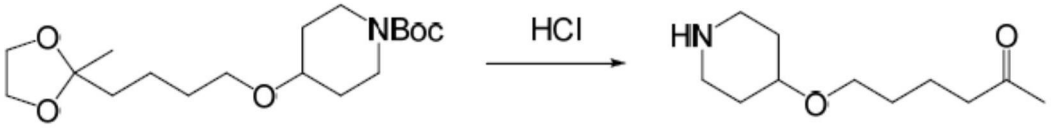
[0449] 于配备有磁力搅拌棒和迪恩-斯达克(Dean-Stark)的经火焰干燥的圆底烧瓶中,在N_2下,将含于甲苯(40mL)中的6-溴-己-2-酮(2.0g,11.17mmol)、乙二醇(6.93g,111.7mmol)和TsOH(384mg,0.22mmol)的溶液加热至回流持续3小时。允许将反应冷却至室温,和添加饱和$NaHCO_3$水溶液(60mL)和乙酸乙酯(100mL)。将有机层分离,用水(2x 100mL)洗涤,经$MgSO_4$干燥,过滤和于真空中浓缩。将残余物通过硅胶柱(石油醚:EtOAc 4:1)纯化以得到呈无色油的所需产物2-(4-溴丁基)-2-甲基-1,3-二氧戊环(1.6g)。产率64%(98%纯度,UV=214nm,ESI未发现)。^{1}H-NMR(400MHz,$CDCl_3$)δ1.34(s,3H),1.50-1.65(m,2H),1.65-1.75(m,2H),1.84-1.98(m,2H),3.43(t,J=6.8Hz,2H),3.90-4.04(m,4H)。

[0450] 步骤3:4-(4-(2-甲基-1,3-二氧戊环-2-基)丁氧基)哌啶-1-甲酸叔丁酯

[0451] 

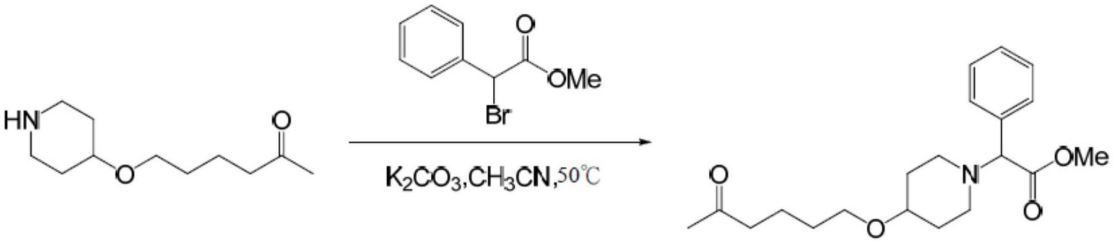
[0452] 在0℃下，将含于DMF(10mL)中的4-羟基哌啶-1-甲酸叔丁酯(866mg，4.31mmol)和NaH(287mg，7.18mmol)的混合物搅拌1小时。在0℃下，将含于DMF(5mL)中的2-(4-溴丁基)-2-甲基-1,3-二氧戊环(800mg，3.59mmol)的溶液逐滴添加至以上混合物中，和将反应混合物在100℃下搅拌过夜。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 1:1)纯化以得到呈无色油的所需产物4-(4-(2-甲基-1,3-二氧戊环-2-基)丁氧基)哌啶-1-甲酸叔丁酯(420mg)。产率36%(98%纯度，UV＝214nm，ESI 243$(M+H)^+$)。

[0453] 步骤4：6-(哌啶-4-基氧基)己-2-酮

[0454] 

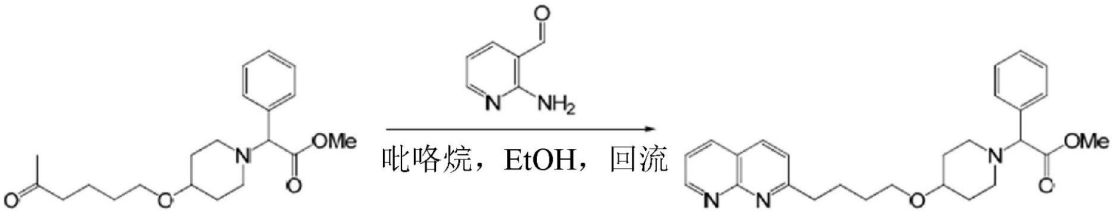
[0455] 在室温下，将4-(4-(2-甲基-1,3-二氧戊环-2-基)丁氧基)哌啶-1-甲酸叔丁酯(420mg，1.22mmol)用含于1,4-二噁烷(10mL)中的4M HCl(3.1mL，12.2mmol)处理2小时。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 1:2)纯化以得到呈无色油的所需产物6-(哌啶-4-基氧基)己-2-酮(290mg)。产率97%(98%纯度，UV＝214nm，ESI 243$(M+H)^+$)。

[0456] 步骤5：2-(4-(5-氧代基己氧基)哌啶-1-基)-2-苯基乙酸甲酯

[0457] 

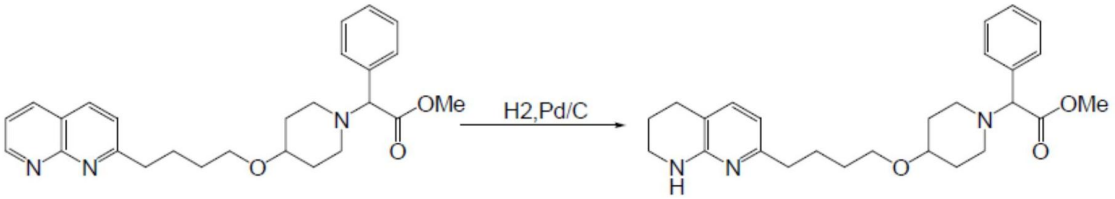
[0458] 在50℃下，将含于乙腈(8mL)中的6-(哌啶-4-基氧基)己-2-酮(290mg，1.19mmol)、K_2CO_3(493mg，3.57mmol)和2-溴-2-苯基乙酸甲酯(409mg，1.79mmol)的混合物搅拌3小时。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 1:2)纯化以得到呈无色油的所需产物2-(4-(5-氧代基己氧基)哌啶-1-基)-2-苯基乙酸甲酯(340mg)。产率82%(98%纯度，UV＝214nm，ESI 347$(M+H)^+$)。

[0459] 步骤6：2-(4-(4-(1,8-萘啶-2-基)丁氧基)哌啶-1-基)-2-苯基乙酸甲酯

[0460] 

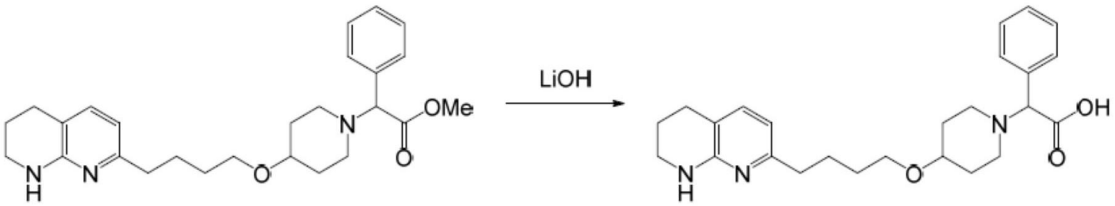
[0461] 将含于乙醇(8mL)中的2-(4-(5-氧代基己氧基)哌啶-1-基)-2-苯基乙酸甲酯(340mg，0.98mmol)、2-氨基烟碱醛(155mg，1.27mmol)和吡咯烷(90mg，1.27mmol)的混合物回流过夜。于真空中去除溶剂，和将残余物通过硅胶柱(DCM:MeOH 40:1)纯化以得到呈无色油的所需产物2-(4-(4-(1,8-萘啶-2-基)丁氧基)哌啶-1-基)-2-苯基乙酸甲酯(220mg)。产率51%(98%纯度，UV＝254nm，ESI 434.5(M+H)+)。

[0462] 步骤7：2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)哌啶-1-基)乙酸甲酯

[0463] 

[0464] 在气球氢气下，在室温下，将含于EtOAc(30mL)中的2-(4-(4-(1,8-萘啶-2-基)丁氧基)哌啶-1-基)-2-苯基乙酸甲酯(220mg，0.51mmol)和Pd/C(10%，20mg)的混合物搅拌16小时。将混合物过滤和浓缩以得到呈无色油的所需产物(220mg)。产率99%(92%纯度，UV＝214nm，ESI 438.4(M+H)+)。

[0465] 步骤8：2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)哌啶-1-基)乙酸(化合物12-E1和12-E2)(MRT-B0103)

[0466] 

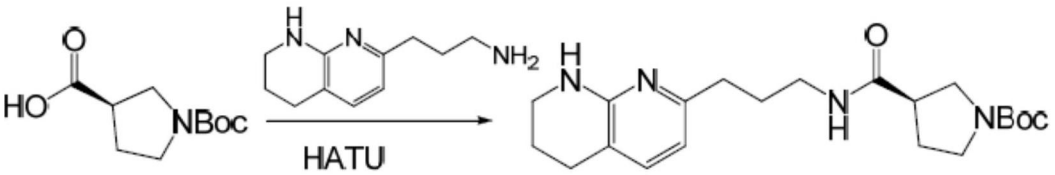
[0467] 在室温下，将2-(4-(4-(1,8-萘啶-2-基)丁氧基)哌啶-1-基)-2-苯基乙酸甲酯(220mg，0.51mmol)用含于MeOH(4mL)和H_2O(1mL)中的LiOH-H_2O(86mg，2.04mmol)处理2小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的外消旋化合物12(42mg，19%产率)。将所述外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物12-E1(17mg)和化合物12-E2(20mg)。

[0468] 化合物12-E1 LC/MS A：98%纯度，UV＝214nm，Rt＝1.61min，ESI 423.5(M+H)+。^{1}H-NMR(400MHz，MeOD)δ7.61-7.50(m,2H)，7.48-7.38(m,3H)，7.14(d,J＝7.3Hz,1H)，6.36(d,J＝7.3Hz,1H)，4.46(s,1H)，3.57(s,1H)，3.46(t,J＝6.2Hz,2H)，3.41-3.35(m,2H)，3.14(s,1H)，2.85(s,1H)，2.71(t,J＝6.2Hz,2H)，2.53(t,J＝7.5Hz,2H)，2.19-1.79(m,7H)，1.56-1.63(m,5H)。手性SFC A(45%MeOH)：ee 96.2%，Rt＝1.88min。

[0469] 化合物12-E2 LC/MS A：97%纯度，UV＝214nm，Rt＝1.61min，ESI 423.5(M+H)+。^{1}H-NMR(400MHz，MeOD)δ7.61-7.50(m,2H)，7.48-7.38(m,3H)，7.14(d,J＝7.3Hz,1H)，6.36(d,J＝7.3Hz,1H)，4.46(s,1H)，3.57(s,1H)，3.46(t,J＝6.2Hz,2H)，3.41-3.35(m,2H)，3.14(s,1H)，2.85(s,1H)，2.71(t,J＝6.2Hz,2H)，2.53(t,J＝7.5Hz,2H)，2.19-1.79(m,7H)，1.56-1.63(m,5H)。手性SFC A(45%MeOH)：ee 99.6%，Rt＝3.05min。

[0470] 实例13：制备2-苯基-2-((R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-基)乙酸(化合物13-E1和13-E2)

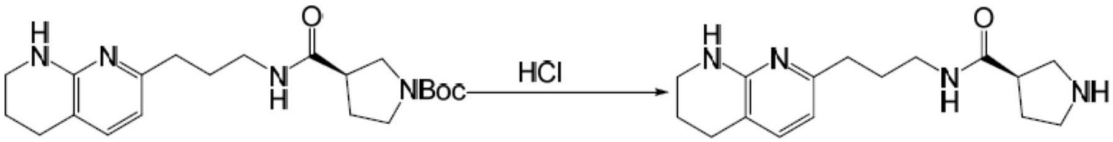
[0471] 步骤1：(R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-甲酸叔丁酯

[0472] 

[0473] 将含于DMF(5.0mL)中的(R)-1-(叔丁氧羰基)吡咯烷-3-甲酸(124.7mg，

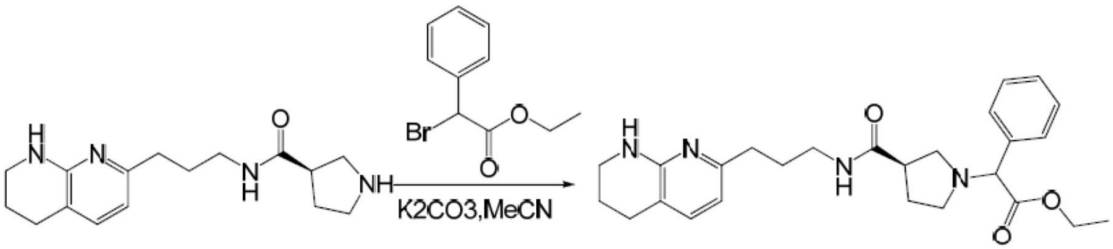
0.58mmol)、3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙-1-胺(100mg,0.52mmol)、HATU(331mg,0.87mmol)和DIPEA(374mg,2.9mmol)的混合物在室温下搅拌2小时。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 10:1)纯化以得到呈黄色油的所需产物(R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-甲酸叔丁酯(110mg)。产率49%(ESI 389(M+H)+)。

[0474] 步骤2:(R)-N-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)吡咯烷-3-甲酰胺

[0475] 

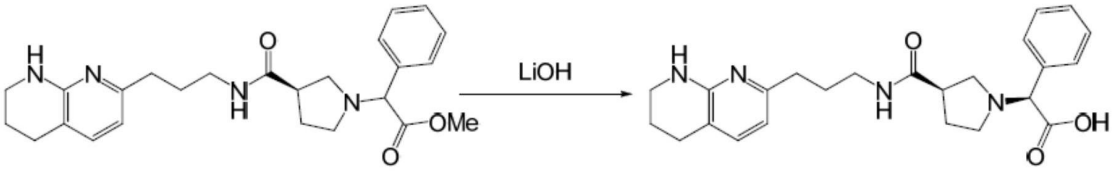
[0476] 在室温下,将(R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-甲酸叔丁酯(110mg,0.29mmol)用HCl/二噁烷的溶液(4.0M,2mL)处理2小时。于真空中去除溶剂以得到呈棕色油的所需产物(80mg)。产率98%(ESI 289.2(M+H)+)。

[0477] 步骤3:2-苯基-2-((R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-基)乙酸乙酯

[0478] 

[0479] 将含于MeCN(2.5mL)中的(R)-N-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)吡咯烷-3-甲酰胺(80mg,0.28mmol)、2-溴-2-苯基乙酸乙酯(68.6mg,0.28mmol)和K_2CO_3(116mg,0.84mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物2-苯基-2-((R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-基)乙酸乙酯(70mg)。产率71%(ESI 451.3$(M+H)^+$)。

[0480] 步骤4:2-苯基-2-((R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-基)乙酸(化合物13-E1和13-E2)

[0481] 

[0482] 在室温下,将2-苯基-2-((R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)吡咯烷-1-基)乙酸乙酯(70mg,0.16mmol)用含于MeOH(2.0mL)和H_2O(0.5mL)中的LiOH-H_2O(65.1mg,1.55mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的两种非对映异构体化合物13-E1(6.1mg)和化合物13-E2(6.5mg)。

[0483] 化合物13-E1 LC/MS B:100%纯度,UV=214nm,Rt=1.23min,ESI423.7(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.55-7.46(m,2H),7.45-7.29(m,3H),7.24(d,J=7.2Hz,1H),6.42(d,J=7.2Hz,1H),4.17(s,1H),3.43-3.37(m,3H),3.25-3.12(m,2H),2.97-2.50(m,8H),2.31-

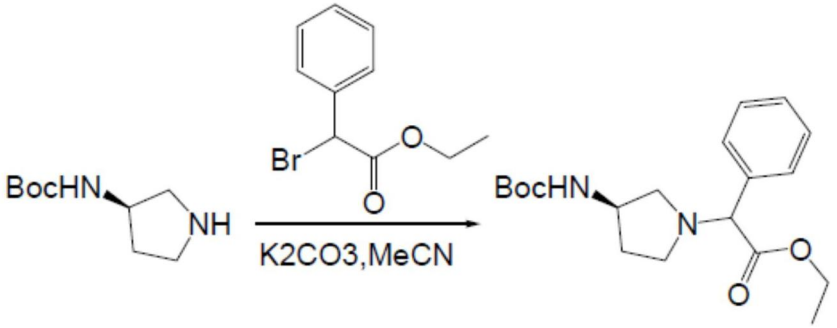
2.19(m,1H),2.05-1.73(m,5H)。

[0484] 化合物13-E2 LC/MS B:97%纯度,UV=214nm,Rt=1.23min,ESI423.7(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.54-7.53(m,2H),7.39-7.24(m,3H),7.16(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.04(s,1H),3.38(t,J=5.6Hz,2H),3.28-3.18(m,2H),3.05-2.83(m,4H),2.71(t,J=6.2Hz,2H),2.58-2.52(m,3H),2.09-1.87(m,6H)。

[0485] 实例14:2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)吡咯烷-1-基)乙酸(化合物14)

[0486] 步骤1:2-((R)-3-(叔丁氧羰基氨基)吡咯烷-1-基)-2-苯基乙酸乙酯

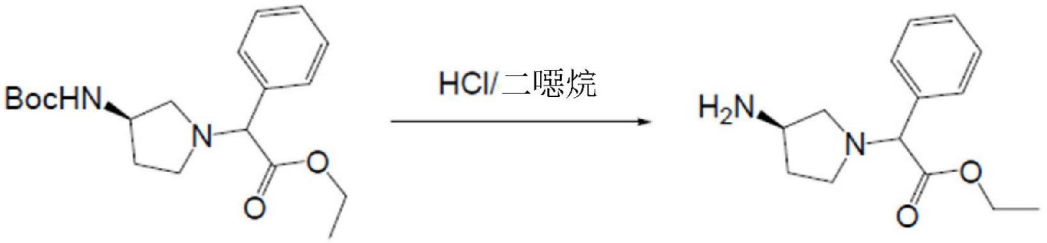
[0487]



[0488] 将含于MeCN(5mL)中的(R)-吡咯烷-3-基氨基甲酸叔丁酯(200mg,1.07mmol)、2-溴-2-苯基乙酸乙酯(390mg,1.60mmol)和K_2CO_3(445mg,3.22mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 3:1)纯化以得到呈黄色油的所需产物2-((R)-3-(叔丁氧羰基氨基)吡咯烷-1-基)-2-苯基乙酸乙酯(335mg)。产率89%(ESI 349.0(M+H)$^+$)。

[0489] 步骤2:2-((R)-3-氨基吡咯烷-1-基)-2-苯基乙酸乙酯

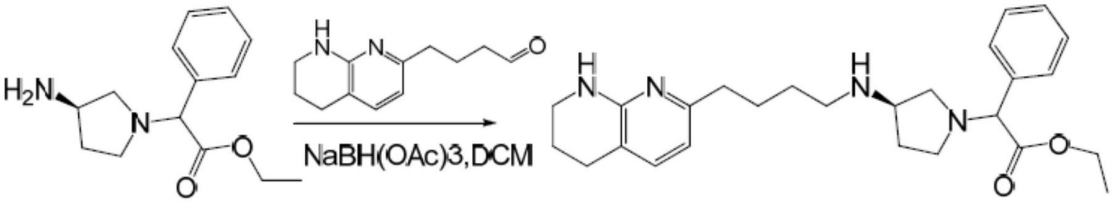
[0490]



[0491] 在室温下,将2-((R)-3-(叔丁氧羰基氨基)吡咯烷-1-基)-2-苯基乙酸乙酯(335mg,0.96mmol)用HCl/二噁烷的溶液(4.0M,4mL)处理2小时,然后于真空中去除溶剂以得到呈棕色油的所需产物2-((R)-3-氨基吡咯烷-1-基)-2-苯基乙酸乙酯(234mg)。产率98%(ESI 249.2(M+H)+)。

[0492] 步骤3:2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)吡咯烷-1-基)乙酸乙酯

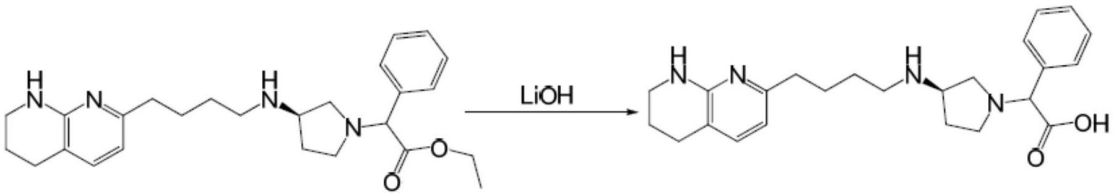
[0493]



[0494] 将含于DCM(5mL)中的2-((R)-3-氨基吡咯烷-1-基)-2-苯基乙酸乙酯(234mg,0.94mmol)、4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁醛(191mg,0.94mmol)和$NaBH(OAc)_3$

(598mg,2.82mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 15:1)纯化以得到呈无色油的所需2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)吡咯烷-1-基)乙酸乙酯(180mg)。产率44%(ESI 437(M+H)+)。

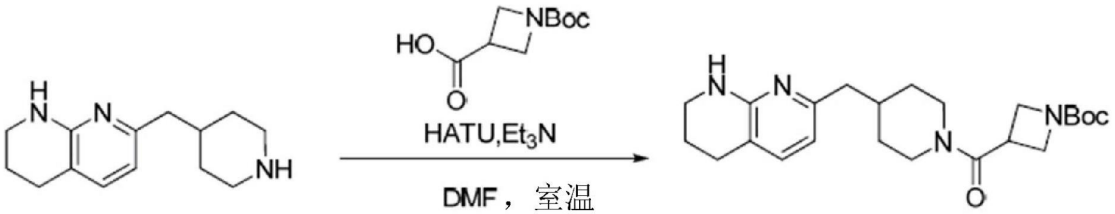
[0495] 步骤4:2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)吡咯烷-1-基)乙酸(化合物14)

[0496] 

[0497] 在室温下,将2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)吡咯烷-1-基)乙酸乙酯(180mg,0.41mmol)用含于MeOH(5.0mL)和H_2O(1.0mL)中的LiOH-H_2O(86mg,2.05mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈黄色固体的化合物14(52mg)。LC/MS E:98%纯度,UV=214nm,Rt=1.03min,ESI 409.2(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.61-7.54(m,2H),7.54-7.20(m,3H),7.15(d,J=7.3Hz,1H),6.42-6.38(m,1H),3.81-3.77(m,1H),3.62-3.51(m,1H),3.43-3.34(m,2H),3.24-3.20(m,1H),2.94-2.20(m,9H),1.88-1.57(m,8H)。

[0498] 实例15:制备2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(化合物15)

[0499] 步骤1:3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯

[0500] 

[0501] 将含于DMF(2mL)中的1-(叔丁氧羰基)氮杂环丁烷-3-甲酸(132mg,0.66mmol)、HATU(251mg,0.66mmol)、7-(哌啶-4-基甲基)-1,2,3,4-四氢-1,8-萘啶盐酸盐(200mg,0.66mmol)和三乙胺(0.4mL,2.64mmol)的混合物搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 0:100)纯化以得到呈浅黄色固体的3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯(210mg)。产率77%(100%纯度,UV=214nm,ESI 415$(M+H)^+$)。

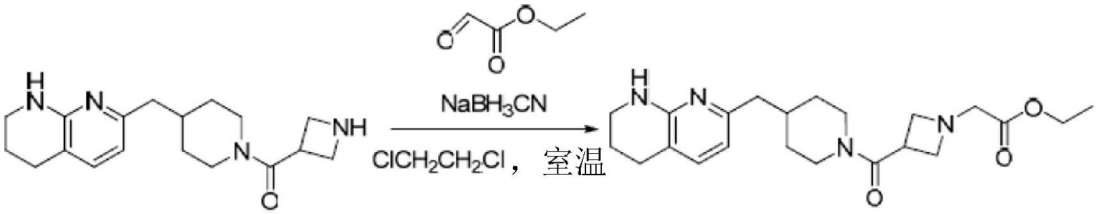
[0502] 步骤2:氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮

[0503] 

[0504] 在室温下,将3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯(210mg,0.51mmol)用含于二噁烷(2mL)中的HCl(2mL,8mmol)处理过夜。

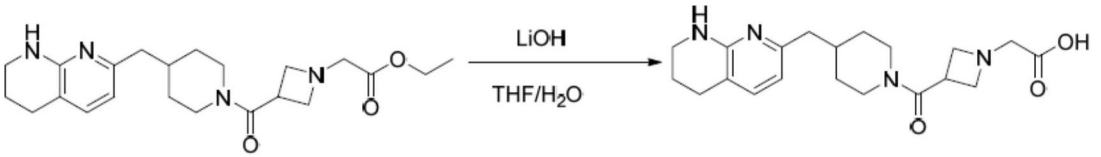
于真空中去除溶剂以得到呈浅黄色固体的氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮(189mg)。产率100%(100%纯度,UV=214nm,ESI 315(M+H)$^+$)。

[0505] 步骤3:2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸乙酯

[0506] 

[0507] 在室温下,将$NaBH_3CN$(103mg,6.63mmol)添加至经搅拌的含于DCE中的氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮(158mg,0.41mmol)和2-氧代基乙酸乙酯(0.1mL,0.12mmol)的混合物中。将所得混合物搅拌2小时,然后用水(20mL)稀释和用DCM(3×20mL)萃取。将合并的有机萃取物用水、盐水洗涤,干燥和浓缩以得到呈浅黄色油的2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸乙酯(150mg)。产率92%(100%纯度,UV=214nm,ESI 401(M+H)$^+$)。

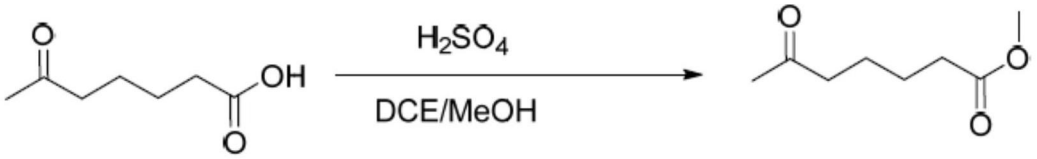
[0508] 步骤4:2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(化合物15)

[0509] 

[0510] 在室温下,将2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸乙酯(163mg,0.41mmol)用含于THF(4mL)和H_2O(2mL)中的LiOH-H_2O(34mg,0.81mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的化合物15(15mg)。产率10%(LC/MS A:100%纯度,UV=214nm,Rt=1.44min,ESI 373(M+H)$^+$)。^{1}H NMR(500MHz,MeOD)δ7.05(d,J=7.2Hz,1H),6.25(d,J=7.2Hz,1H),4.36(d,J=13.1Hz,1H),4.21-4.03(m,3H),3.88-3.77(m,1H),3.63(s,2H),3.48(d,J=13.2Hz,1H),3.32-3.24(m,2H),2.90(t,J=13.1Hz,1H),2.63-2.49(m,3H),2.36(d,J=7.2Hz,2H),1.78(m,3H),1.58(d,J=13.1Hz,2H),1.05(m,2H)。

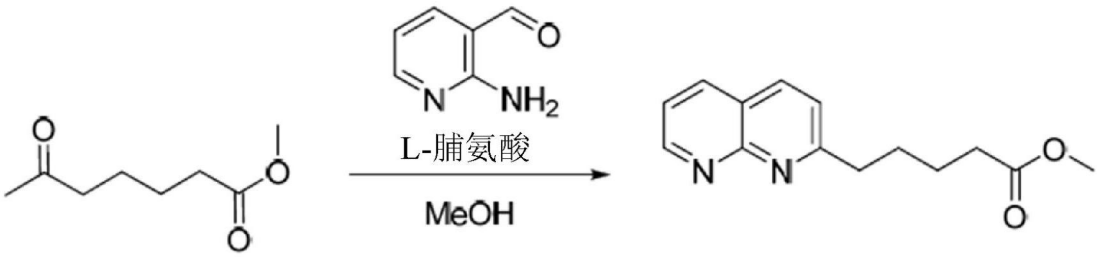
[0511] 实例16:制备2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸(化合物16)

[0512] 步骤1:6-氧代基庚酸甲酯

[0513] 

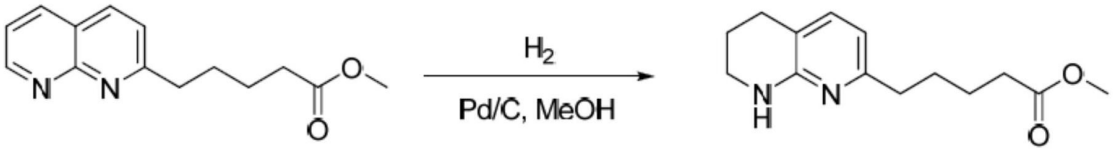
[0514] 将浓H_2SO_4(0.2mL)添加至经搅拌的含于DCE/MeOH(50mL/20mL)中的6-氧代基庚酸(10g,69mmol)的溶液中。将混合物在90℃下搅拌过夜。将溶液冷却至室温和浓缩。将残余物用DCM(200mL)稀释,用饱和$NaHCO_3$溶液、水、盐水洗涤,干燥和浓缩以得到呈浅黄色液体的6-氧代基庚酸甲酯(8.4g)产率76%(100%纯度,UV=214nm,ESI 159(M+H)$^+$)。

[0515] 步骤2:5-(1,8-萘啶-2-基)戊酸甲酯

[0516] 

[0517] 在90℃下,将含于MeOH(100mL)中的6-氧代基庚酸甲酯(11g,69.53mmol)、2-氨基烟碱醛(8.5g,69.53mmol)和L-脯氨酸(4g,34.77mmol)的混合物搅拌过夜。将混合物冷却至室温和浓缩。将粗产物通过硅胶柱(EtOAc)纯化以得到呈浅黄色固体的5-(1,8-萘啶-2-基)戊酸甲酯(7g)。产率65%(100%纯度,UV=214nm,ESI 245$(M+H)^+$)。^{1}H NMR(400MHz,$CDCl_3$)δ 9.08(dd,J=4.2,1.9Hz,1H),8.16(dd,J=8.1,1.9Hz,1H),8.10(d,J=8.3Hz,1H),7.44(dd,J=8.1,4.3Hz,1H),7.39(d,J=8.3Hz,1H),3.66(s,3H),3.11-3.02(m,2H),2.39(m,2H),1.96(m,2H),1.81-1.70(m,2H)。

[0518] 步骤3:5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊酸甲酯

[0519] 

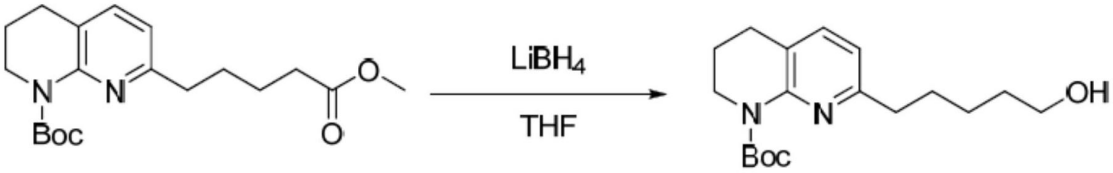
[0520] 在气球H_2下,在室温下,将含于MeOH(50mL)中的5-(1,8-萘啶-2-基)戊酸甲酯(5g,20.47mmol)和Pd/C(500mg)的混合物搅拌过夜。将混合物过滤和浓缩以得到呈浅棕色油的5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊酸甲酯(4.2g)。产率83%(100%纯度,UV=214nm,ESI 249$(M+H)^+$)。

[0521] 步骤4:7-(5-甲氧基-5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯

[0522] 

[0523] 在80℃下,将含于二噁烷(20mL)中的5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊酸甲酯(2.4g,9.7mmol)和Boc_2O(11g,8mmol)的混合物搅拌16小时。将混合物浓缩,和将残余物通过硅胶柱色谱法(石油醚:EtOAc 1:1)纯化以得到呈浅黄色油的7-(5-甲氧基-5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(1.8g),产率53%(100%纯度,UV=214nm,ESI 349$(M+H)^+$)。

[0524] 步骤5:7-(5-羟戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯

[0525] 

[0526] 在75℃下,将含于THF(10mL)中的7-(5-甲氧基-5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(740mg,2.12mmol)和$LiBH_4$(93mg,4.24mmol)的混合物搅拌2小时。将

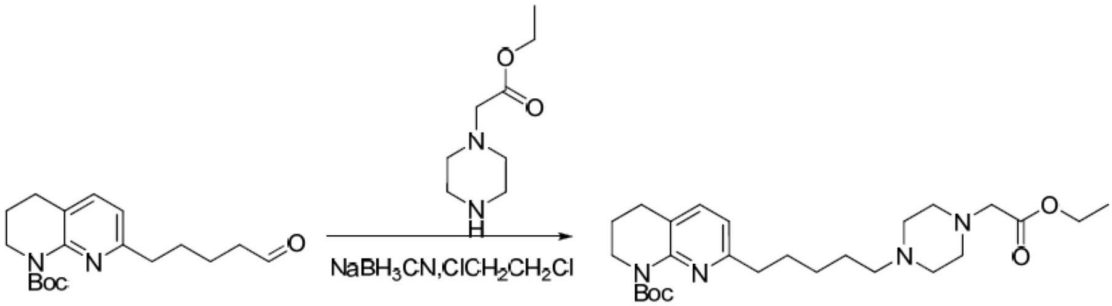
溶液冷却至室温和浓缩，用EtOAc(20mL)稀释，用水和盐水洗涤，干燥和浓缩以得到呈浅黄色油的7-(5-羟戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(500mg)。产率73%(100%纯度，UV=214nm，ESI 321$(M+H)^+$)。

[0527] 步骤6：7-(5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯

[0528] 

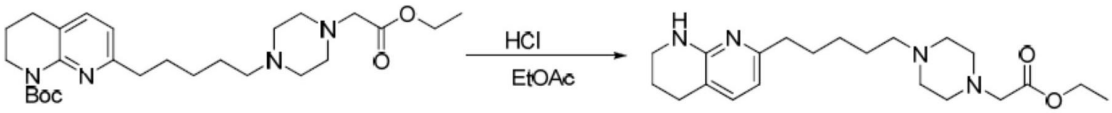
[0529] 将IBX(1.22g，4.36mmol)添加至DMSO(15mL)中并搅拌直至溶液变得澄清。向所述溶液中逐滴添加含于DMSO(5mL)中的7-(5-羟戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(700mg，2.18mmol)，和将所得混合物在室温下搅拌16小时，然后用水(80mL)稀释和用DCM(300mL)萃取。将合并的有机萃取物用水和盐水洗涤，干燥和浓缩。将残余物通过硅胶柱色谱法(石油醚:EtOAc 1:1)纯化以得到呈浅黄色油的7-(5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(498mg)产率72%(100%纯度，UV=214nm，ESI 319$(M+H)^+$)。

[0530] 步骤7：7-(5-(4-(2-乙氧基-2-氧代基乙基)哌嗪-1-基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯

[0531] 

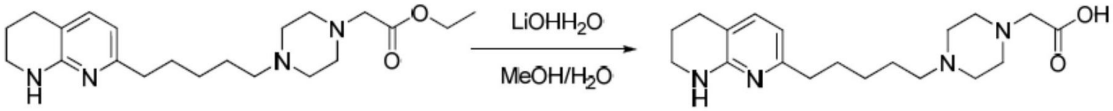
[0532] 在室温下，将$NaBH_3CN$(79mg，1.26mmol)添加至经搅拌的含于DCE中的7-(5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(100mg，0.31mmol)和2-(哌嗪-1-基)乙酸乙酯(81mL，0.47mmol)的混合物中。将所得混合物搅拌2小时，然后用水(20mL)稀释和用DCM(3×20mL)萃取。将合并的有机萃取物用水和盐水洗涤，干燥和浓缩以得到呈浅黄色油的7-(5-(4-(2-乙氧基-2-氧代基乙基)哌嗪-1-基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(98mg)。产率65%(100%纯度，UV=214nm，ESI 475$(M+H)^+$)。

[0533] 步骤8：2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸乙酯

[0534] 

[0535] 在室温下，将7-(5-(4-(2-乙氧基-2-氧代基乙基)哌嗪-1-基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(20mg，0.04mmol)用含于二噁烷(2mL)中的HCl(3mL，9mmol)处理过夜。于真空中去除溶剂以得到呈浅黄色固体的2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸乙酯(10mg)。产率63%(100%纯度，UV=214nm，ESI 375$(M+H)^+$)。

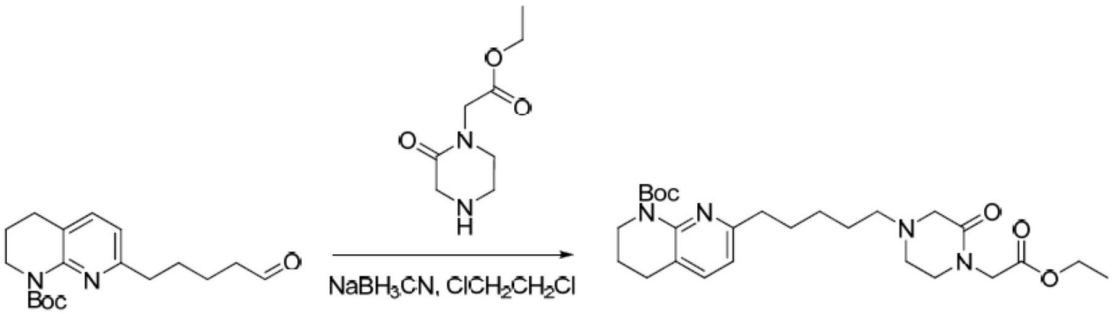
[0536] 步骤9：2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸(化合物16)

[0537] 

[0538] 在室温下，将2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸乙酯(10mg，0.03mmol)用含于THF(4mL)和H_2O(2mL)中的LiOH-H_2O(3.4mg，0.09mmol)处理2小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物16(5mg)。产率54%(LC/MS A:100%纯度，UV＝214nm，Rt＝1.45min，ESI 347 $(M+H)^+$)。^{1}H NMR(500MHz，MeOD)δ7.14(d，J＝7.3Hz，1H)，6.38(d，J＝7.3Hz，1H)，3.42-3.36(m，2H)，3.10(s，2H)，2.81-2.56(m，10H)，2.53(t，J＝7.6Hz，2H)，2.46-2.40(m，2H)，1.92-1.83(m，2H)，1.71-1.62(m，2H)，1.61-1.51(m，2H)，1.40-1.30(m，2H)。

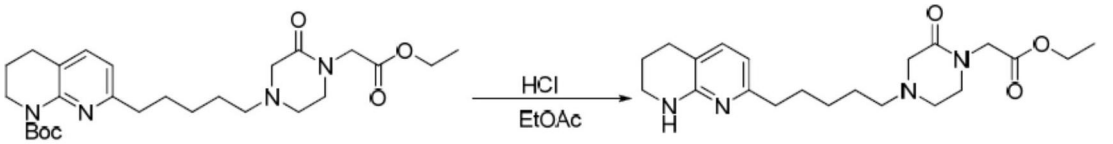
[0539] 实例17:2-(2-氧代基-4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸(化合物17)

[0540] 步骤1:7-(5-(4-(2-乙氧基-2-氧代基乙基)-3-氧代基哌嗪-1-基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯

[0541] 

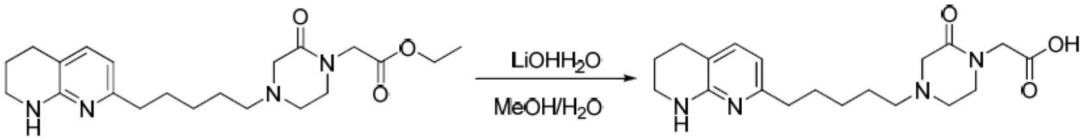
[0542] 在室温下，将$NaBH_3CN$(79mg，1.24mmol)添加至经搅拌的含于DCE中的7-(5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(100mg，0.31mmol)和2-(2-氧代基哌嗪-1-基)乙酸乙酯(175mg，0.93mmol)的混合物中。将所得混合物搅拌2小时，然后用水(20mL)稀释和用DCM(3×20mL)萃取。将合并的有机萃取物用水和盐水洗涤，干燥和浓缩以得到呈浅黄色油的7-(5-(4-(2-乙氧基-2-氧代基乙基)-3-氧代基哌嗪-1-基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(50mg)。产率32%(100%纯度，UV＝214nm，ESI 489 $(M+H)^+$)。

[0543] 步骤2:2-(2-氧代基-4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸乙酯

[0544] 

[0545] 在室温下，将7-(5-(4-(2-甲氧基-2-氧代基乙基)-3-氧代基哌嗪-1-基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(50mg，0.11mmol)用含于二噁烷(2mL)中的HCl(3mL，9mmol)处理过夜。于真空中去除溶剂以得到呈浅黄色固体的2-(2-氧代基-4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸乙酯(34mg)。产率87%(100%纯度，UV＝214nm，ESI 389 $(M+H)^+$)。

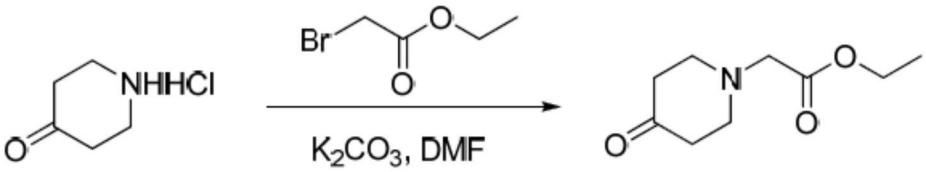
[0546] 步骤3:2-(2-氧代基-4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸(化合物17)

[0547] 

[0548] 在室温下，将2-(2-氧代基-4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)乙酸乙酯(38mg，0.10mmol)用含于THF(4mL)和H_2O(2mL)中的LiOH-H_2O(13mg，0.30mmol)处理2小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(33至65％MeCN)纯化以得到呈白色固体的化合物17(18mg)。产率48％(LC/MS A：100％纯度，UV＝214nm，Rt＝0.95min，ESI 361$(M+H)^+$)。^{1}H NMR(500MHz，MeOD)δ7.46(d，J＝7.3Hz，1H)，6.52(d，J＝7.3Hz，1H)，3.98(s，2H)，3.52(t，J＝5.7Hz，2H)，3.49-3.43(m，2H)，3.30(s，2H)，3.00(t，J＝5.7Hz，2H)，2.79(t，J＝6.1Hz，2H)，2.77-2.70(m，2H)，2.69-2.61(m，2H)，1.98-1.87(m，2H)，1.77-1.67(m，2H)，1.67-1.58(m，2H)，1.54(m，2H)。

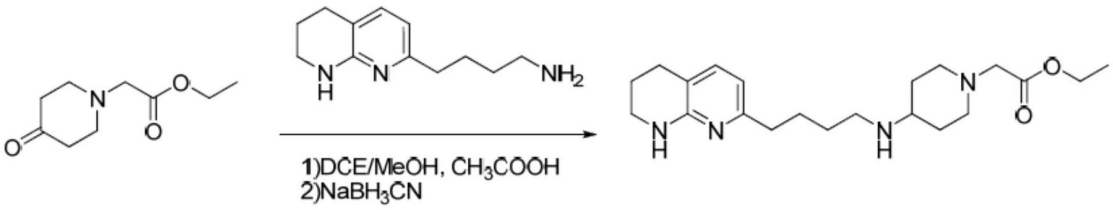
[0549] 实例18：制备2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸(化合物18)

[0550] 步骤1：2-(4-氧代基哌啶-1-基)乙酸乙酯

[0551] 

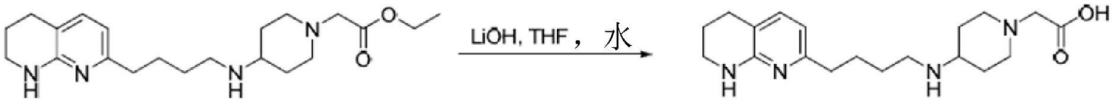
[0552] 将含于DMF(4mL)中的哌啶-4-酮盐酸盐(120mg，0.88mmol)、K_2CO_3(245mg，1.76mmol)和2-溴乙酸乙酯(147mg，0.88mmol)的混合物在室温下搅拌2小时。将反应混合物用水(20mL)稀释和用EtOAc(15mL x3)萃取。将合并的有机萃取物用盐水洗涤，经Na_2SO_4干燥和浓缩以得到呈黄色油的2-(4-氧代基哌啶-1-基)乙酸乙酯(140mg，85％产率)。(89％纯度，UV＝214nm，ESI 186.2$(M+H)^+$)。

[0553] 步骤2：2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸乙酯

[0554] 

[0555] 向含于DCE(2mL)和MeOH(2mL)中的2-(4-氧代基哌啶-1-基)乙酸乙酯(140mg，0.75mmol)的溶液中添加4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁-1-胺(155mg，0.75mmol)和乙酸(1滴)。将反应混合物在室温下搅拌1小时。然后添加$NaBH_3CN$(190mg，3mmol)，和将反应混合物在室温下搅拌2小时。将反应混合物于真空中浓缩，和将残余物通过硅胶柱(MeOH：EtOAc＝1：5)纯化以得到呈黄色油的2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸乙酯(120mg，42％产率)。(100％纯度，UV＝214nm，ESI＝375.3$(M+H)^+$)。

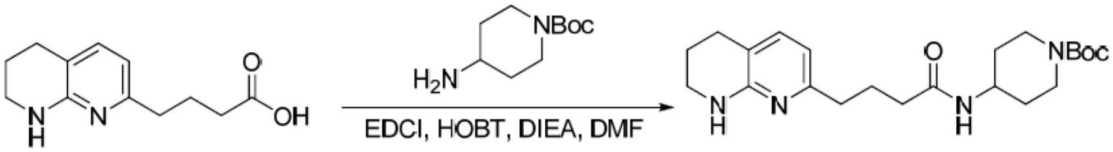
[0556] 步骤3：2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸(化合物18)

[0557] 

[0558] 在室温下，将2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸乙酯(120mg，0.32mmol)用含于THF(4mL)和水(2mL)中的LiOH(23mg，0.96mmol)处理2小时。将反应混合物用6N HCl中和和于真空中浓缩，和将残余物通过制备型HPLC A(35至69%MeCN)纯化以得到呈白色固体的化合物18(57mg)。LC/MS A：100%纯度，UV＝214nm，Rt＝1.47min，ESI 347.3$(M+H)^+$。^{1}H NMR(500MHz，CD_3OD)δ7.18(d，J＝7.2Hz，1H)，6.42(d，J＝7.2Hz，1H)，3.38-3.33(m，2H)，3.33-3.32(m，4H)，3.01-2.96(m，3H)，2.69(t，J＝6Hz，2H)，2.56(t，J＝7.2Hz，2H)，2.46(t，J＝11.6Hz，2H)，2.08(m，2H)，1.86(m，2H)，1.67(m，6H)

[0559] 实例19：制备2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸(化合物19)

[0560] 步骤1：4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-甲酸叔丁酯

[0561] 

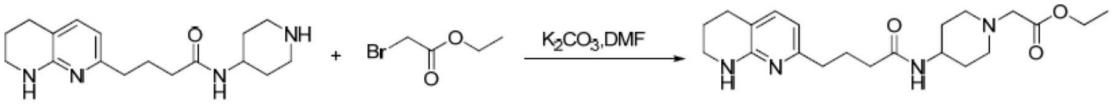
[0562] 向含于DMF(4mL)中的4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酸(100mg，0.46mmol)的溶液中添加4-氨基哌啶-1-甲酸叔丁酯(110mg，0.55mmol)、EDCI(104mg，0.55mmol)、HOBT(73mg，0.55mmol)和DIEA(117mg，0.92mmol)。将反应混合物在室温下搅拌2小时。将反应混合物用水(25mL)稀释和用EtOAc(15mL，3次)萃取。将合并的有机相用盐水洗涤，经Na_2SO_4干燥和于真空中浓缩以得到呈黄色油的4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-甲酸叔丁酯(120mg，66%产率)。(80%纯度，UV＝254nm，ESI 403.2$(M+H)^+$)。

[0563] 步骤2：N-(哌啶-4-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺

[0564] 

[0565] 向含于DCM(4mL)中的4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-甲酸叔丁酯(120mg，0.29mmol)的溶液中添加TFA(4mL)。将反应混合物在室温下搅拌2小时。将反应于真空中浓缩，和将残余物通过制备型HPLC A(30至60%MeCN)纯化以得到呈黄色油的N-(哌啶-4-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺(87mg，98%产率)。(100%纯度，UV＝254nm，ESI 303.3$(M+H)^+$)。

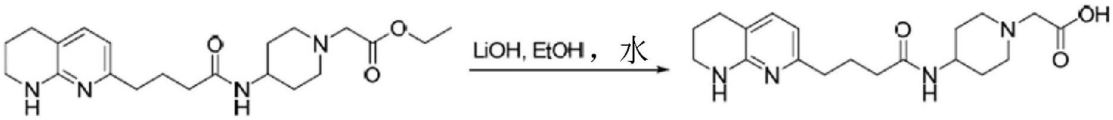
[0566] 步骤3：2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸乙酯

[0567] 

[0568] 将含于DMF(3mL)中的N-(哌啶-4-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺(87mg，0.29mmol)、2-溴乙酸乙酯(52mg，0.32mmol)和K_2CO_3(47mg，0.32mmol)的混合物在室温下搅拌2小时。将反应混合物用水(30mL)稀释和用EtOAc(15mL，3x)萃取。将合并的有机相用盐水洗涤，经Na_2SO_4干燥和于真空中浓缩，和将残余物通过硅胶柱(MeOH:EtOAc＝5:1)纯

化以得到呈黄色油的2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸乙酯(70mg,62%产率)。(100%纯度,UV=254nm,ESI 389.1$(M+H)^+$)。

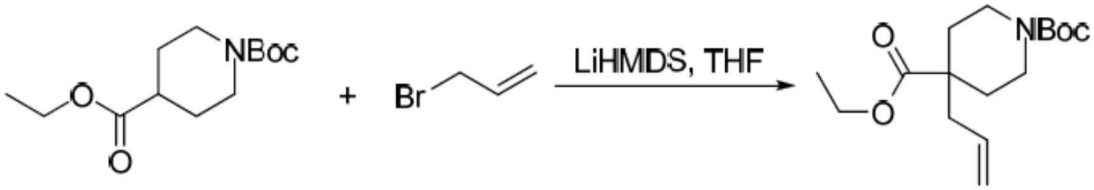
[0569] 步骤4:2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸(化合物19)

[0570] 

[0571] 在室温下,将2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸乙酯(70mg,0.18mmol)用含于EtOH(4mL)和水(2mL)中的LiOH(21mg,0.9mmol)处理2小时。将反应混合物用6N HCl中和。将所得混合物于真空中浓缩,和将残余物通过制备型HPLC A(35至69%MeCN)纯化以得到呈白色固体的化合物19(47.3mg)。LC/MS A:100%纯度,UV=214nm,Rt=1.47min,ESI 361.3(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.18(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),3.99-3.85(m,1H),3.61-3.49(m,4H),3.41(dd,J=14.9,9.4Hz,2H),3.10(t,J=11.0Hz,2H),2.73-2.70(m,2H),2.56(t,J=7.6Hz,2H),2.32-2.18(m,2H),2.10-2.07(m,2H),2.00-1.74(m,6H)。

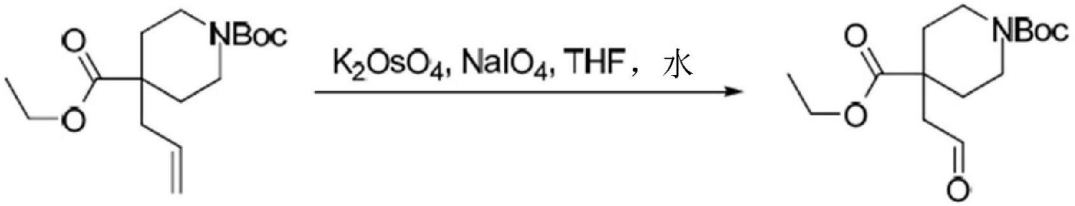
[0572] 实例20:制备2-(1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-基)乙酸(化合物20)

[0573] 步骤1:4-烯丙基哌啶-1,4-二甲酸1-叔丁酯4-乙酯

[0574] 

[0575] 在-78℃下,向含于THF(50mL)中的哌啶-1,4-二甲酸1-叔丁酯4-乙酯(5g,19.5mmol)的溶液中添加LiHMDS(25.3mL,1M/L含于THF中,25.3mmol)。将反应混合物在-78℃下搅拌1小时。然后在-78℃下添加3-溴丙-1-烯(3.5g,29.3mmol),和将反应混合物在室温下搅拌16小时。将反应混合物用水(30mL)稀释和用EtOAc(50mL)萃取。将有机相于真空中浓缩,和将残余物通过硅胶柱(石油醚:EtOAc=10:1)纯化以得到呈无色油的4-烯丙基哌啶-1,4-二甲酸1-叔丁酯4-乙酯(5g,86%产率)。(86%纯度,UV=214nm,ESI 242.2$(M-55)^+$)。

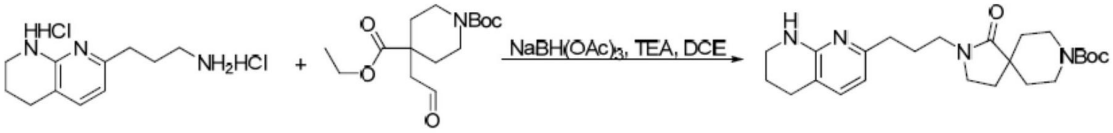
[0576] 步骤2:4-(2-氧代基乙基)哌啶-1,4-二甲酸1-叔丁酯4-乙酯

[0577] 

[0578] 向含于THF(20mL)和水(10mL)中的4-烯丙基哌啶-1,4-二甲酸1-叔丁酯4-乙酯(1g,3.36mmol)的溶液中添加含于水(2mL)中的K_2OsO_4(60mg,0.17mmol)的溶液。将反应混合物在室温下搅拌1小时。然后添加含于水(8mL)中的$NaIO_4$(1.44g,6.72mmol)的溶液,和将反应混合物在室温下搅拌2小时。将反应用DCM(3x 20mL)萃取。将合并的有机相用盐水洗涤,经Na_2SO_4干燥和于真空中浓缩以得到呈黑色油的4-(2-氧代基乙基)哌啶-1,4-二甲酸1-叔

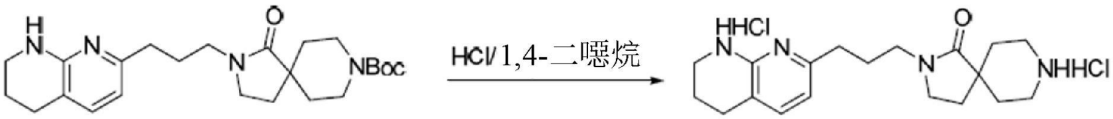
丁酯4-乙酯(1g,100%粗物质产率)。(36%纯度,UV=214nm,ESI 200.2(M-99)$^+$)。

[0579] 步骤3:1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-甲酸叔丁酯

[0580] 

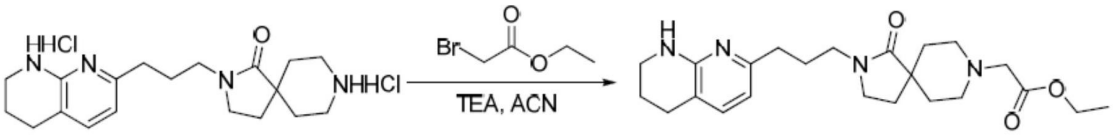
[0581] 向含于DCE(10mL)中的3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙-1-胺二盐酸盐(400mg,1.52mmol)的悬浮液中添加三乙胺(383mg,3.8mmol)和4-(2-氧代基乙基)哌啶-1,4-二甲酸1-叔丁酯4-乙酯(454mg,1.52mmol)。将反应混合物在室温下搅拌1小时。然后添加$NaBH(OAc)_3$(644mg,3.04mmol),和将反应混合物在室温下搅拌48小时。将反应混合物于真空中浓缩,和将残余物通过硅胶柱(EtOAc:MeOH=4:1)纯化以得到呈黄色油的1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-甲酸叔丁酯(300mg,46%产率)。(60%纯度,UV=254nm,ESI 429.3(M+H)$^+$)。

[0582] 步骤4:2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-1-酮二盐酸盐

[0583] 

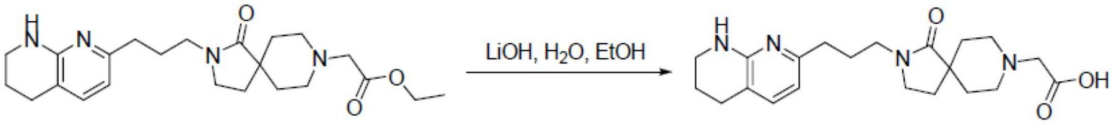
[0584] 在0℃下,向含于1,4-二噁烷(4mL)中的1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-甲酸叔丁酯(300mg,0.7mmol)的溶液中添加含于1,4-二噁烷中的HCl(6mL,4M,24mmol)。将反应混合物在室温下搅拌16小时。将反应于真空中浓缩以得到呈黄色油的2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-1-酮二盐酸盐(400mg,100%产率)。(83%纯度,UV=254nm,ESI 329.4(M+H)$^+$)。

[0585] 步骤5:2-(1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-基)乙酸乙酯

[0586] 

[0587] 向含于ACN(7mL)中的2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-1-酮二盐酸盐(400mg,1mmol)的溶液中添加三乙胺(300mg,3mmol)和2-溴乙酸乙酯(193mg,0.75mmol)。将反应混合物在室温下搅拌2小时。将反应混合物于真空中浓缩,和将残余物通过硅胶柱(MeOH:EtOAc=1:5)分离以得到呈黄色固体的2-(1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-基)乙酸乙酯(180mg,产率45%)。(75%纯度,UV=254nm,ESI 415.4(M+H)$^+$)。

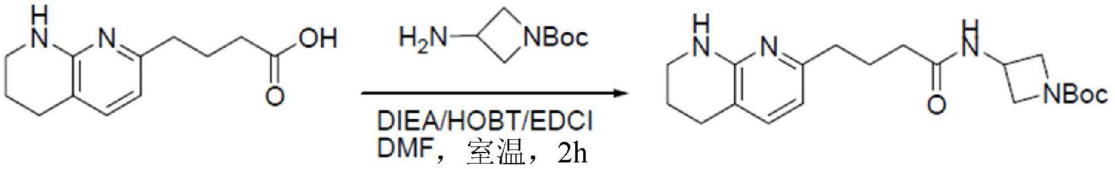
[0588] 步骤6:2-(1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-基)乙酸(化合物20)

[0589] 

[0590] 在室温下，将2-(1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,8-二氮杂螺[4.5]癸烷-8-基)乙酸乙酯(180mg，0.43mmol)用含于EtOH(4mL)和水(2mL)中的LiOH(92mg，2.17mmol)处理2小时。将反应用2N HCl中和和于真空中浓缩，和将残余物通过制备型HPLC A(35至65%MeCN)纯化以得到呈白色固体的化合物20(70mg)。LC/MS A:100%纯度，UV＝214nm，Rt＝1.45min，ESI 387.4$(M+H)^+$。^{1}H NMR(500MHz，CD_3OD)δ7.14(d，J＝7Hz，1H)，6.39(d，J＝7Hz，1H)，3.50-3.33(m，10H)，3.01(br，2H)，2.71(t，J＝6.5Hz，2H)，2.51(t，J＝7Hz，2H)，2.09-2.01(m，4H)，1.91-1.86(m，4H)，1.69(d，J＝13Hz，2H)。

[0591] 实例21：制备2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-基)乙酸(化合物21)

[0592] 步骤1：3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-甲酸叔丁酯

[0593] 

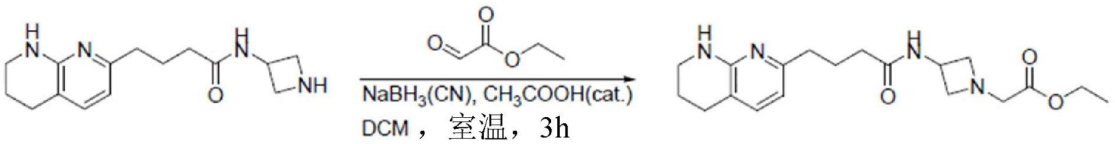
[0594] 将含于DMF(2mL)中的4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酸(100mg，0.45mmol)、3-氨基氮杂环丁烷-1-甲酸叔丁酯(78.2mg，0.45mmol)、EDCI(123mg，0.72mmol)、HOBT(48.6mg，0.36mmol)和DIEA(290mg，2.25mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂，和将残余物通过硅胶柱(MeOH:EtOAc 1:10)纯化以得到呈黄色油的所需产物3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-甲酸叔丁酯(80mg)。产率47%(98%纯度，UV＝214nm，ESI 375$(M+H)^+$)。

[0595] 步骤2：N-(氮杂环丁烷-3-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺

[0596] 

[0597] 在室温下，将3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-甲酸叔丁酯(80mg，0.21mmol)用含于DCM(3mL)中的TFA(3mL，1.06mmol)处理过夜。于真空中去除溶剂，和将残余物通过硅胶柱(DCM:MeOH 40:1)纯化以得到呈黄色油的所需产物N-(氮杂环丁烷-3-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺(205mg)。产率98%(98%纯度，UV＝214nm，ESI 275$(M+H)^+$)。

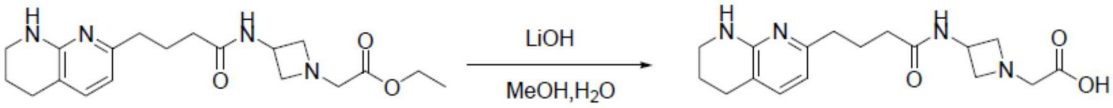
[0598] 步骤3：2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-基)乙酸乙酯

[0599] 

[0600] 将含于DCM(5mL)中的N-(氮杂环丁烷-3-基)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰胺(60mg，0.20mmol)、2-氧代基乙酸乙酯(82mg，0.80mmol)、乙酸(0.12mg，0.002mmol)和$NaBH(OAc)_3$(127.2mg，0.60mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂，和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈无色油的所需产物2-(3-(4-(5,6,7,8-

四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-基)乙酸乙酯(30mg)。产率38%(98%纯度,UV=214nm,ESI 361$(M+H)^+$)。

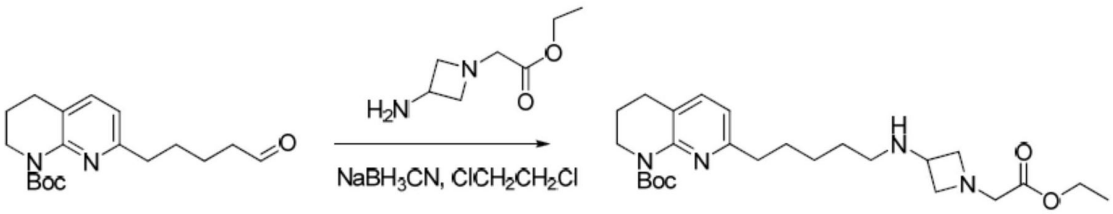
[0601] 步骤4:2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-基)乙酸(化合物21)

[0602] 

[0603] 在室温下,将2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-基)乙酸乙酯(30mg,0.083mmol)用含于MeOH(1mL)和H_2O(1mL)中的LiOH-H_2O(14mg,0.33mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的化合物21(10mg)。产率33%。LC/MS A:98%纯度,Rt=1.46min,ESI 333$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.16(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.55(p,J=7.3Hz,1H),4.23-4.15(m,2H),3.78(dd,J=10.4,7.0Hz,2H),3.43-3.37(m,2H),2.72(t,J=6.2Hz,2H),2.56(t,J=7.5Hz,2H),2.24(t,J=7.5Hz,2H),2.00-1.85(m,4H)。

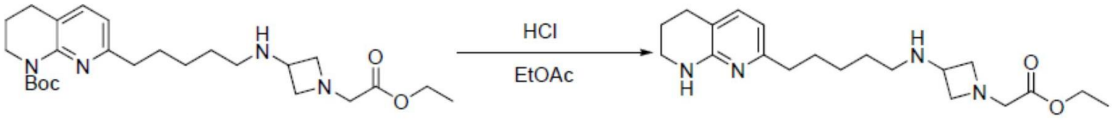
[0604] 实例22:2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氨基)氮杂环丁烷-1-基)乙酸(化合物22)

[0605] 步骤1:7-(5-(1-(2-乙氧基-2-氧代基乙基)氮杂环丁烷-3-基氨基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯

[0606] 

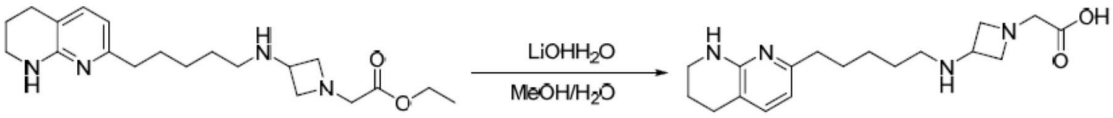
[0607] 在室温下,将$NaBH_3CN$(59mg,0.94mmol)添加至经搅拌的含于DCE中的7-(5-氧代基戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(100mg,0.31mmol)和2-(3-氨基氮杂环丁烷-1-基)乙酸乙酯盐酸盐(73mg,0.38mmol)的混合物中。将所得混合物在室温下搅拌2小时,然后用水(20mL)稀释和用DCM(3×20mL)萃取。将合并的有机萃取物用水和盐水洗涤,干燥和浓缩以得到呈浅黄色油的7-(5-(1-(2-乙氧基-2-氧代基乙基)氮杂环丁烷-3-基氨基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(102mg)。产率71%(100%纯度,UV=214nm,ESI 461$(M+H)^+$)。

[0608] 步骤2:2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氨基)氮杂环丁烷-1-基)乙酸乙酯

[0609] 

[0610] 在室温下,将7-(5-(1-(2-乙氧基-2-氧代基乙基)氮杂环丁烷-3-基氨基)戊基)-3,4-二氢-1,8-萘啶-1(2H)-甲酸叔丁酯(35mg,0.08mmol)用含于二噁烷(2mL)中的HCl(3mL,9mmol)处理过夜。于真空中去除溶剂以得到呈浅黄色固体的2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氨基)氮杂环丁烷-1-基)乙酸乙酯(20mg)。产率73%(100%纯度,UV=214nm,ESI 361$(M+H)^+$)。

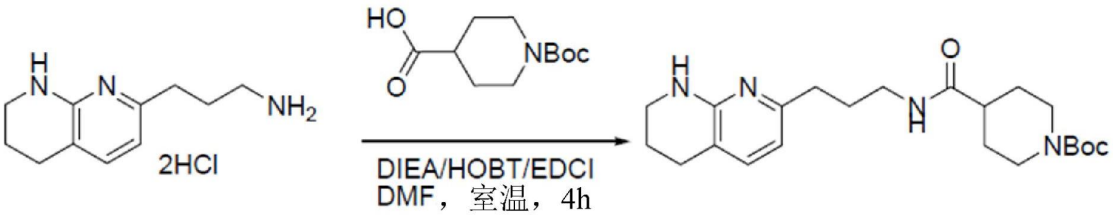
[0611] 步骤3:2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氨基)氮杂环丁烷-1-基)乙酸(化合物22)

[0612] 

[0613] 在室温下,将2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氨基)氮杂环丁烷-1-基)乙酸乙酯(25mg,0.07mmol)用含于THF(2mL)和H_2O(2mL)中的LiOH-H_2O(9mg,0.21mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLCB(33至65%MeCN)纯化以得到呈白色固体的化合物22(5mg)产率26%(LC/MS A:100%纯度,UV=214nm,Rt=1.47min,ESI 333$(M+H)^+$)。^{1}H NMR(500MHz,MeOD)δ8.45(s,2H),7.52(d,J=7.3Hz,1H),6.56(d,J=7.3Hz,1H),4.37-4.21(m,2H),4.00-3.91(m,2H),3.88(m,1H),3.78(s,2H),3.52-3.41(m,2H),2.81(t,J=6.1Hz,2H),2.70(dd,J=16.0,8.2Hz,4H),2.03-1.87(m,2H),1.81-1.65(m,2H),1.67-1.52(m,2H),1.51-1.37(m,2H)。

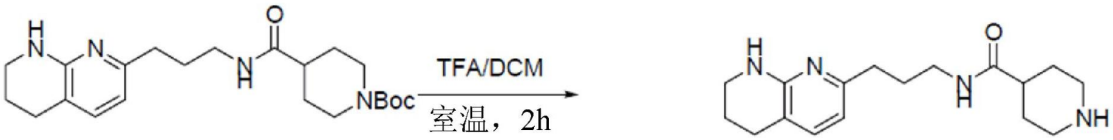
[0614] 实例23:2-苯基-2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸(化合物23-E1和23-E2)

[0615] 步骤1:4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-甲酸叔丁酯

[0616] 

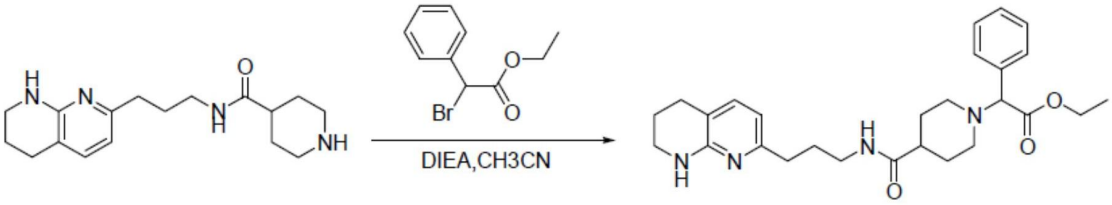
[0617] 将含于DMF(4mL)中的3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙-1-胺(200mg,0.76mmol)、1-(叔丁氧羰基)哌啶-4-甲酸(173mg,0.76mmol)、EDCI(234.2mg,1.22mmol)、HOBT(82.1mg,0.61mmol)和DIEA(490.2mg,3.8mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(MeOH:EtOAc1:10)纯化以得到呈黄色油的所需产物4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-甲酸叔丁酯(133mg)。产率43%(98%纯度,UV=214nm,ESI 403.0$(M+H)^+$)。

[0618] 步骤2:N-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)哌啶-4-甲酰胺

[0619] 

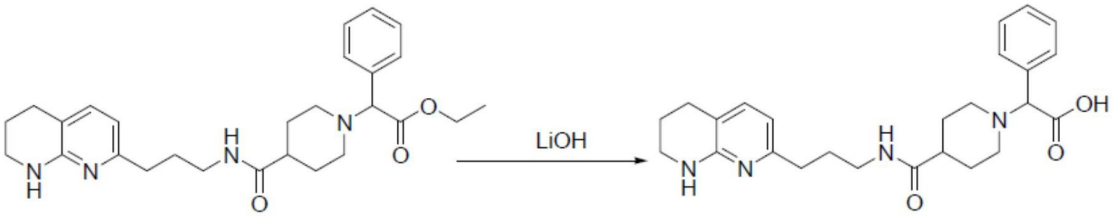
[0620] 在室温下,将4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-甲酸叔丁酯(133mg,0.33mmol)用含于DCM(5mL)中的TFA(5mL,1.65mmol)处理过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 40:1)纯化以得到呈黄色油的所需产物N-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)哌啶-4-甲酰胺(100mg)。产率99%(98%纯度,UV=214nm,ESI 303$(M+H)^+$)。

[0621] 步骤3:2-苯基-2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸乙酯

[0622] 

[0623] 将含于MeCN(4mL)中的N-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)哌啶-4-甲酰胺(200mg,0.66mmol)、2-溴-2-苯基乙酸乙酯(192mg,0.79mmol)和DIEA(255mg,1.98mmol)的混合物在室温下搅拌3小时。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈黄色油的所需产物2-苯基-2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸乙酯(200mg)。产率65%(98%纯度,UV=214nm,ESI 465$(M+H)^+$)。

[0624] 步骤4:2-苯基-2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸(化合物23-E1和23-E2)(MRT-C0123)

[0625] 

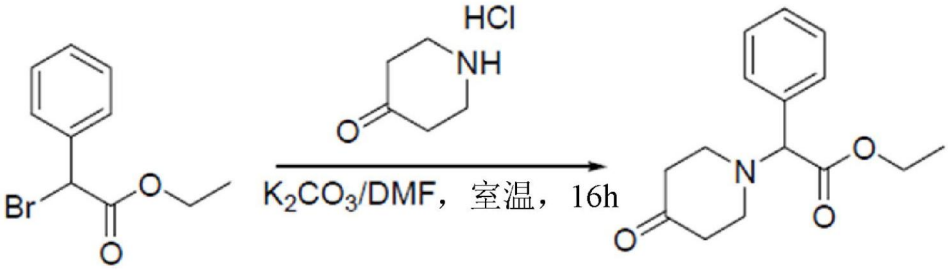
[0626] 在50℃下,将2-苯基-2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸乙酯(200mg,0.43mmol)用含于MeOH(4mL)和H_2O(2mL)中的LiOH-H_2O(88.3mg,2.15mmol)处理3小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的外消旋化合物23(150mg,44%产率)。将所述外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物23-E1(40mg)和化合物23-E2(44mg)。

[0627] 化合物23-E1 LC/MS A:98%纯度,UV=214nm,Rt=1.48min,ESI437$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.59(dd,J=6.5,2.8Hz,2H),7.49-7.41(m,3H),7.16(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.43(s,1H),3.77(s,1H),3.41-3.36(m,2H),3.20(t,J=6.9Hz,2H),3.06(s,1H),2.95(t,J=10.0Hz,1H),2.82(s,1H),2.70(dd,J=13.8,7.5Hz,2H),2.57-2.51(m,2H),2.48-2.38(m,1H),2.10-1.93(m,3H),1.92-1.79(m,5H)。手性S,S-Whelk-O1A(45%MeOH):ee 100%,Rt=2.17min。

[0628] 化合物23-E2 LC/MS A:98%纯度,UV=214nm,Rt=1.48min,ESI437$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.59(dd,J=6.4,2.8Hz,2H),7.48-7.41(m,3H),7.17(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.43(s,1H),3.76(s,1H),3.42-3.36(m,2H),3.20(t,J=6.9Hz,2H),3.06(d,J=11.6Hz,1H),2.94(t,J=10.5Hz,1H),2.80(s,1H),2.71(t,J=6.2Hz,2H),2.58-2.51(m,2H),2.48-2.38(m,1H),2.01(tt,J=22.5,11.2Hz,3H),1.92-1.79(m,5H)。手性S,S-Whelk-O1A(45%MeOH):ee 100%,Rt=3.04min。

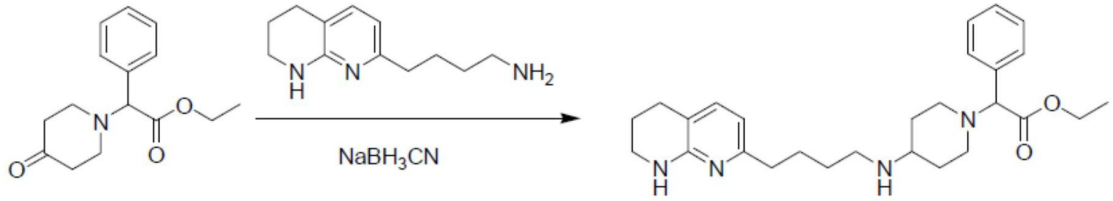
[0629] 实例24:制备2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸(化合物24-E1和24-E2)

[0630] 步骤1:2-(4-氧代基哌啶-1-基)-2-苯基乙酸乙酯

[0631] 

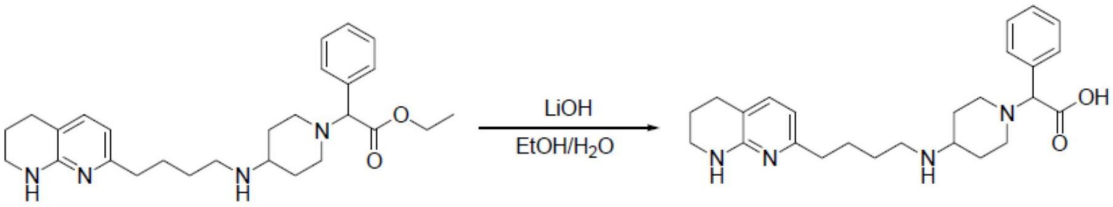
[0632] 将含于DMF(30mL)中的哌啶-4-酮盐酸盐(1.0g,7.38mmol)、2-溴-2-苯基乙酸乙酯(2.53g,11.06mmol)和K_2CO_3(3.06g,22.13mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物2-(4-氧代基哌啶-1-基)-2-苯基乙酸乙酯(1.0g)。产率92%(98%纯度,UV=214nm,ESI 262.0$(M+H)^+$)。

[0633] 步骤2:2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸乙酯

[0634] 

[0635] 将含于DCM(10mL)中的4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁-1-胺(261mg,1.28mmol)、2-(4-氧代基哌啶-1-基)-2-苯基乙酸乙酯(400mg,1.5mmol)和$NaBH_3CN$(245mg,3.84mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈无色油的所需产物2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸乙酯(180mg)。产率45%(98%纯度,UV=214nm,ESI 451$(M+H)^+$)。

[0636] 步骤3:2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸(化合物24-E1和24-E2)

[0637] 

[0638] 在室温下,将2-苯基-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氨基)哌啶-1-基)乙酸乙酯(50mg,0.11mmol)用含于EtOH(2mL)和H_2O(1mL)中的LiOH-H_2O(23.4mg,0.56mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物24(30mg,60%产率)。将外消旋产物通过制备型手性SFC B分离以得到呈白色固体的对映异构产物化合物24-E1(2.2mg)和化合物24-E2(5.7mg)。

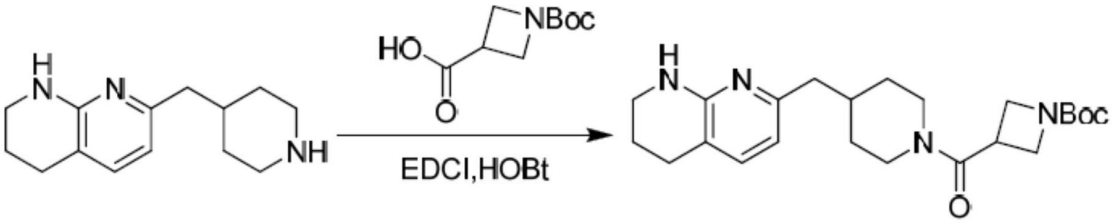
[0639] 化合物24-E1 LC/MS A:100%纯度,UV=214nm,Rt=1.623min,ESI423$(M+H)^{+1}$H NMR(500MHz,MeOD)δ7.52(d,J=7.0Hz,2H),7.34(dt,J=14.1,7.1Hz,3H),7.18(d,J=7.3Hz,1H),6.42(d,J=7.3Hz,1H),3.80(s,1H),3.38-3.34(m,3H),3.04-2.91(m,3H),2.78(s,1H),2.69(t,J=6.2Hz,2H),2.56(t,J=7.0Hz,2H),2.25(s,1H),2.08-1.63(m,11H)。手

性AD-H A(40%MeOH):ee22.5%,Rt=2.49min

[0640] 化合物24-E2 LC/MS A:100%纯度,UV=214nm,Rt=1.51min,ESI423(M+H)$^{+1}$H NMR(500MHz,MeOD)δ7.53(d,J=7.0Hz,2H),7.32(dt,J=21.7,7.0Hz,3H),7.17(d,J=7.3Hz,1H),6.42(d,J=7.3Hz,1H),3.80(s,1H),3.41-3.34(m,3H),3.05-2.88(m,3H),2.79(d,J=11.1Hz,1H),2.69(t,J=6.2Hz,2H),2.56(t,J=7.1Hz,2H),2.25(t,J=11.1Hz,1H),2.08-1.61(m,11H)。手性AD-HA(40%MeOH):ee 36.3%,Rt=0.84min

[0641] 实例25:2-苯基-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(化合物25)

[0642] 步骤1:3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯

[0643] 

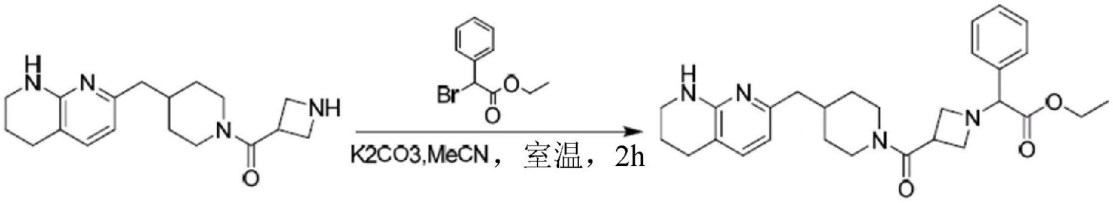
[0644] 将含于DMF(3mL)中的7-(哌啶-4-基甲基)-1,2,3,4-四氢-1,8-萘啶(300mg,0.99mmol)、1-(叔丁氧羰基)氮杂环丁烷-3-甲酸(200mg,0.99mmol)、EDCI(228mg,3.41mmol)、HOBt(135mg,0.99mmol)和DIEA(255mg,1.98mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈黄色油的所需产物3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯(295mg)。产率63%(ESI 415(M+H)$^{+}$)。

[0645] 步骤2:氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮

[0646] 

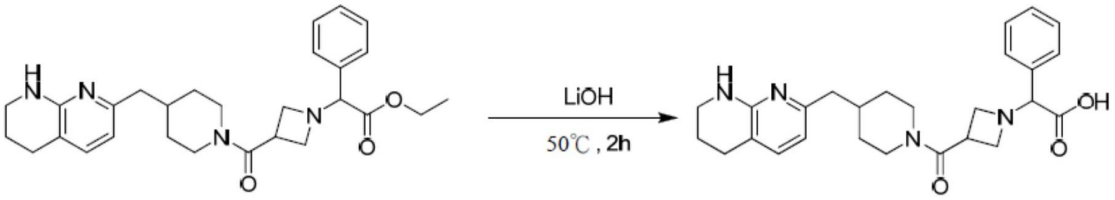
[0647] 在室温下,将3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯(295mg,0.71mmol)用含于1,4-二噁烷(5mL)中的HCl(4mL,15.4mmol)处理过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH40:1)纯化以得到呈黄色油的所需产物氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮(140mg)。产率62%(ESI 315(M+H)$^{+}$)。

[0648] 步骤3:2-苯基-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸乙酯

[0649] 

[0650] 将含于MeCN(5mL)中的哌啶-4-酮盐酸盐(140mg,0.45mmol)、2-溴-2-苯基乙酸乙酯(130mg,0.54mmol)和K_2CO_3(150mg,1.1mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物2-苯基-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸乙酯(130mg)。产率71%(ESI 477$(M+H)^+$)。

[0651] 步骤4:2-苯基-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(化合物25)

[0652] 

[0653] 在50℃下,将2-苯基-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸乙酯(130mg,0.27mmol)用含于EtOH(4mL)和H_2O(1mL)中的LiOH-H_2O(57mg,1.4mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的外消旋化合物25(42mg)。产率34%(ESI 449$(M+H)^+$)。

[0654] 化合物25 LC/MS B:Rt=1.08min,ESI 449(M+H)+。^{1}H NMR(500MHz,CD_3OD)δ7.51(s,2H),7.44(s,3H),7.17(d,J=7.2Hz,1H),6.36(d,J=7.2Hz,1H),4.69(s,1H),4.47(d,J=13.7Hz,1H),4.32(s,1H),4.16(s,1H),4.04(d,J=26.8Hz,1H),3.88(s,2H),3.56(d,J=13.6Hz,1H),3.43-3.37(m,2H),3.00(t,J=12.5Hz,1H),2.72(t,J=6.2Hz,2H),2.66(t,J=12.3Hz,1H),2.47(d,J=7.1Hz,2H),1.98-1.85(m,3H),1.69(d,J=13.1Hz,2H),1.14(d,J=9.0Hz,2H)。

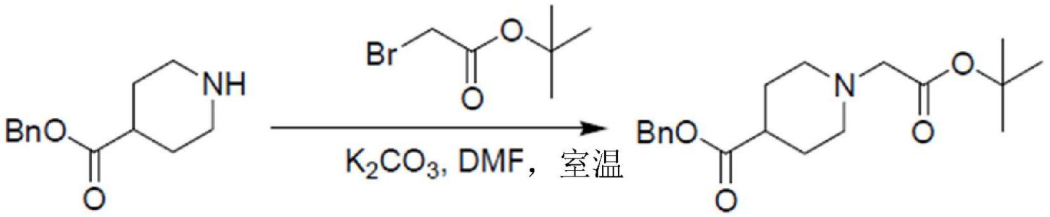
[0655] 实例26:制备2-(4-((3-(6-(甲氨基)吡啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物26)

[0656] 步骤1:哌啶-4-甲酸苄酯

[0657] 

[0658] 在室温下,将哌啶-1,4-二甲酸4-苄酯1-叔丁酯(5g,15.6mmol)用4N HCl/二噁烷(20mL)处理过夜。于真空中去除溶剂以得到呈白色固体的所需产物哌啶-4-甲酸苄酯(4g)。产率100%(100%纯度,UV=214nm,ESI 220$(M+H)^+$)。

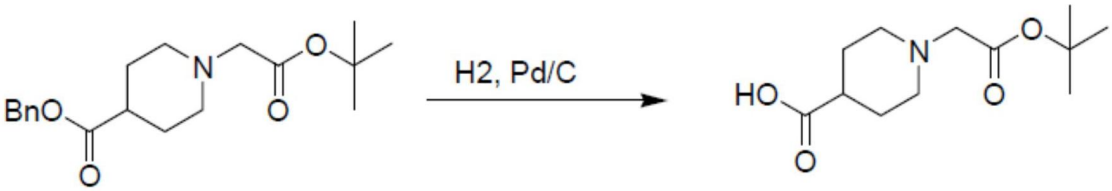
[0659] 步骤2:1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸苄酯

[0660] 

[0661] 将含于DMF(20mL)中的哌啶-4-甲酸苄酯(4g,15mmol)、2-溴乙酸叔丁酯(4.3g,22.5mmol)和K_2CO_3(6.1g,45mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残

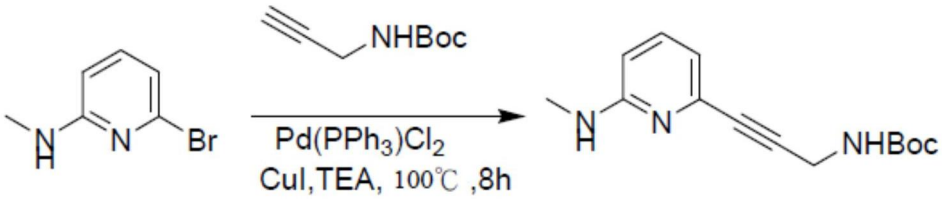
余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸苄酯(3.5g)。产率67%(95%纯度,UV=214nm,ESI 334$(M+H)^+$)。

[0662] 步骤3:1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸

[0663] 

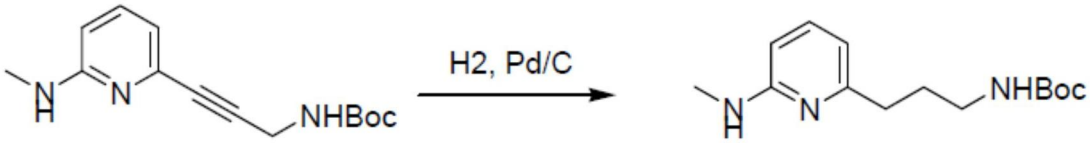
[0664] 在气球氢气下,在室温下,将含于EtOAc(50mL)中的1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸苄酯(3.2g,9.6mmol)和Pd/C(400mg)的混合物搅拌18小时。将混合物过滤和于真空中浓缩以得到呈白色固体的1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸(2.1g)。产率79%(100%纯度,UV=214nm,ESI 244$(M+H)^+$)。

[0665] 步骤4:3-(6-(甲氨基)吡啶-2-基)丙-2-炔基氨基甲酸叔丁酯

[0666] 

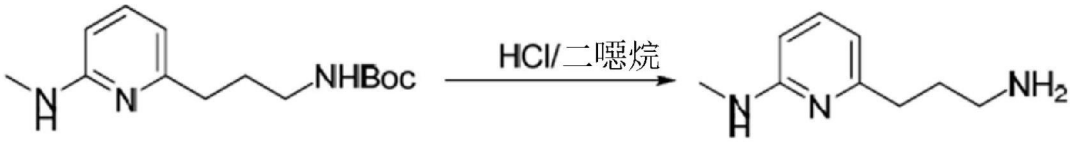
[0667] 在氮气氛围下,在100℃下,将含于DMF(30mL)中的6-溴-N-甲基哌啶-2-胺(600mg,3.2mmol)、Pd$(PPh_3)Cl_2$(141mg,0.3mmol)、CuI(121mg,0.64mmol)、三乙胺(970mg,9.6mmol)和丙-2-炔基氨基甲酸叔丁酯(990mg,6.4mmol)的混合物搅拌8小时。将混合物于真空中浓缩,和将残余物通过硅胶柱(MeOH:DCM1:15)纯化以得到呈无色油的所需产物3-(6-(甲氨基)吡啶-2-基)丙-2-炔基氨基甲酸叔丁酯(500mg)。产率60%(98%纯度,UV=214nm,ESI 262$(M+H)^+$)。

[0668] 步骤5:3-(6-(甲氨基)吡啶-2-基)丙基氨基甲酸叔丁酯

[0669] 

[0670] 在气球氢气下,在室温下,将含于EtOAc(15mL)中的3-(6-(甲氨基)吡啶-2-基)丙-2-炔基氨基甲酸叔丁酯(500mg,1.91mmol)和Pd/C(50mg)的混合物搅拌18小时。将混合物过滤和于真空中浓缩以得到呈黄色油的3-(6-(甲氨基)吡啶-2-基)丙基氨基甲酸叔丁酯(460mg)。产率91%(100%纯度,UV=214nm,ESI266$(M+H)^+$)。

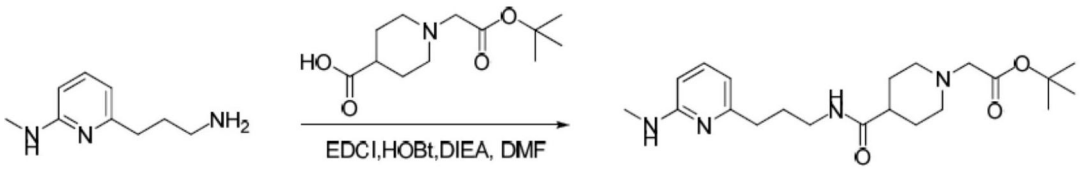
[0671] 步骤6:6-(3-胺丙基)-N-甲基吡啶-2-胺

[0672] 

[0673] 在室温下,将3-(6-(甲氨基)吡啶-2-基)丙基氨基甲酸叔丁酯(460mg,1.73mmol)用4N HCl/二噁烷(10mL)处理14小时。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 7:1)纯化以得到呈黄色油的所需产物6-(3-胺丙基)-N-甲基吡啶-2-胺(280mg)。产率

90%(98%纯度,UV=214nm,ESI 166(M+H)$^+$)。

[0674] 步骤7:2-(4-(3-(6-(甲氨基)吡啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸叔丁酯

[0675] 

[0676] 将含于DMF(4mL)中的6-(3-胺丙基)-N-甲基吡啶-2-胺(120mg,0.73mmol)、1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸(176.7mg,0.73mmol)、EDCI(210mg,1.1mmol)、HOBt(78.8mg,0.58mmol)和DIEA(283mg,2.19mmol)的混合物在室温下搅拌2小时。于真空中去除溶剂,和将残余物通过硅胶柱(MeOH:EtOAc 1:10)纯化以得到呈黄色油的所需产物2-(4-(3-(6-(甲氨基)吡啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸叔丁酯(110mg)。产率39%(98%纯度,UV=214nm,ESI 391(M+H)$^+$)。

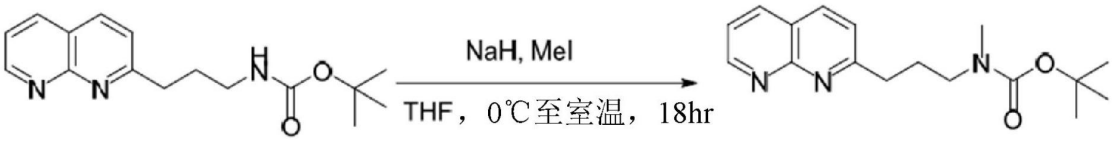
[0677] 步骤8:2-(4-(3-(6-(甲氨基)吡啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸(化合物26)

[0678] 

[0679] 在室温下,将2-(4-(3-(6-(甲氨基)吡啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸叔丁酯(110mg,0.28mmol)用含于DCM(5mL)中的TFA(3mL)处理4小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至70%MeCN)纯化以得到呈白色固体的化合物26。(35.5mg,产率37.9%)。LC/MS A:100%纯度,UV=214nm,Rt=1.30min,ESI 335(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.40(dd,J=8.2,7.5Hz,1H),6.46(d,J=7.2Hz,1H),6.34(d,J=8.4Hz,1H),3.65(d,J=12.3Hz,2H),3.59(s,2H),3.24(t,J=7.0Hz,2H),3.03(td,J=11.9,4.2Hz,2H),2.87(s,3H),2.62(t,J=8.0Hz,2H),2.51-2.46(m,1H),2.09-1.98(m,4H),1.92-1.84(m,2H)。

[0680] 实例27:2-(4-(甲基(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物27)

[0681] 步骤1:3-(1,8-萘啶-2-基)丙基(甲基)氨基甲酸叔丁酯

[0682] 

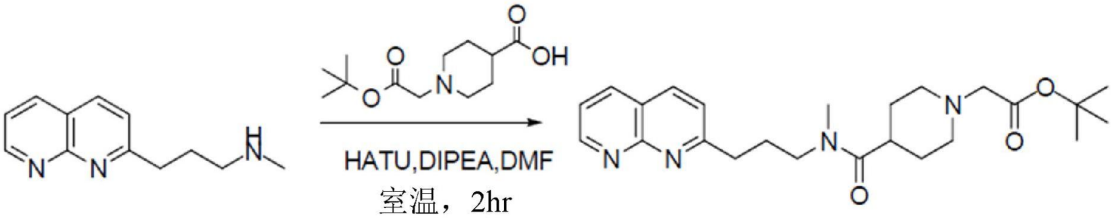
[0683] 在0℃下,向含于无水THF(30mL)中的3-(1,8-萘啶-2-基)丙基氨基甲酸叔丁酯(1g,3.5mmol)的混合物中分部分添加NaH(60%含于矿物油中,0.7g,17.5mmol)。在0℃下,将混合物搅拌30分钟,和然后添加碘甲烷(600mg,4.2mmol)。将混合物在室温下搅拌18小时,然后用水中止,浓缩和通过制备型-HPLC A纯化以得到呈油的所需产物3-(1,8-萘啶-2-基)丙基(甲基)氨基甲酸叔丁酯(180mg)。产率17%(98%纯度,UV=214nm,ESI 302.2(M+H)$^+$)。

[0684] 步骤2:N-甲基-3-(1,8-萘啶-2-基)丙-1-胺

[0685] 

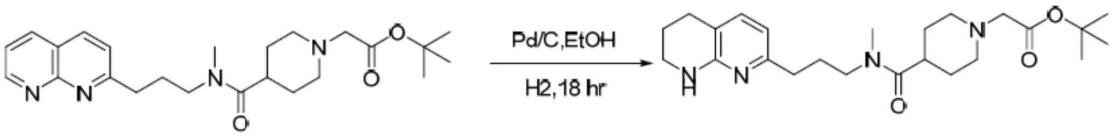
[0686] 在室温下，将3-(1,8-萘啶-2-基)丙基(甲基)氨基甲酸叔丁酯(180mg，0.60mmol)用TFA(5mL)处理3小时。于真空中去除溶剂，和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈黄色油的所需产物N-甲基-3-(1,8-萘啶-2-基)丙-1-胺(110mg)。产率92%(93%纯度，UV＝214nm，ESI 202.2$(M+H)^+$)。

[0687] 步骤3：2-(4-((3-(1,8-萘啶-2-基)丙基)(甲基)氨甲酰基)哌啶-1-基)乙酸叔丁酯

[0688] 

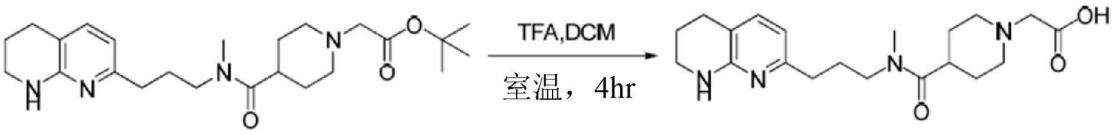
[0689] 将含于DMF(4mL)中的N-甲基-3-(1,8-萘啶-2-基)丙-1-胺(110mg，0.55mmol)、1-(2-叔丁氧基-2-氧代基乙基)哌啶-4-甲酸(134mg，0.55mmol)、HATU(420mg，1.1mmol)和DIPEA(280mg，2.2mmol)的混合物在室温下搅拌2小时。于真空中去除溶剂，和将残余物通过硅胶柱(MeOH:EtOAc 1:10)纯化以得到呈黄色油的所需产物2-(4-((3-(1,8-萘啶-2-基)丙基)(甲基)氨甲酰基)哌啶-1-基)乙酸叔丁酯(120mg)。产率52%(98%纯度，UV＝214nm，ESI 427.0$(M+H)^+$)。

[0690] 步骤4：2-(4-(甲基(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸叔丁酯

[0691] 

[0692] 在H_2(1atm，1L)下，在室温下，将含于EtOH(15mL)中的2-(4-((3-(1,8-萘啶-2-基)丙基)(甲基)氨甲酰基)哌啶-1-基)乙酸叔丁酯(120mg，0.28mmol)和Pd/C(25mg)的混合物搅拌18小时。将混合物过滤和于真空中浓缩以得到呈油的2-(4-(甲基(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸叔丁酯(100mg)。产率83%(100%纯度，UV＝214nm，ESI 431.1$(M+H)^+$)。

[0693] 步骤5：2-(4-(甲基(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物27)

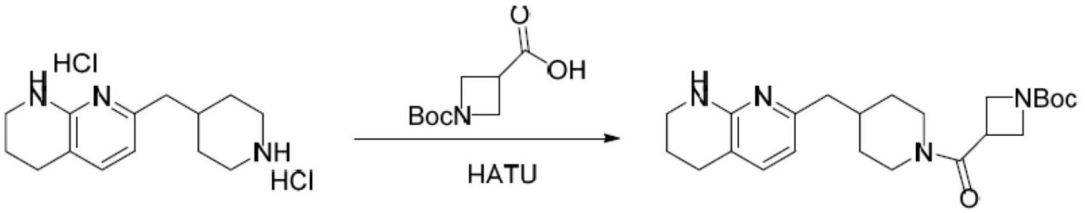
[0694] 

[0695] 在室温下，将2-(4-(甲基(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸叔丁酯(100mg，0.28mmol)用含于DCM(5mL)中的TFA(3mL)处理4小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化

合物27。(9mg,产率10%)。LC/MS A:99%纯度,UV=214nm,Rt=1.41min,ESI 375.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ8.33(s,1H),7.38(d,J=7.1Hz,1H),6.49(d,J=7.4Hz,1H),3.61(d,J=11.2Hz,2H),3.55(s,2H),3.38(dd,J=13.8,6.8Hz,4H),3.11-2.80(m,6H),2.70(dd,J=14.2,8.1Hz,2H),2.55(t,J=7.6Hz,2H),2.02-1.76(m,8H)。

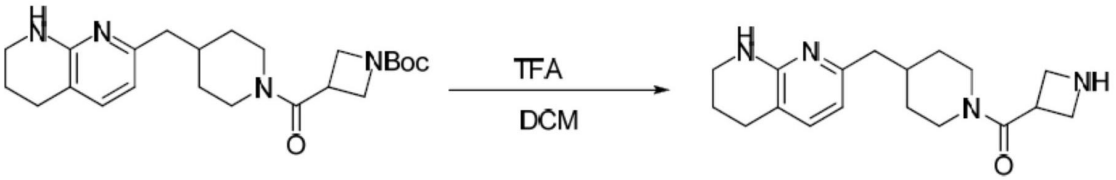
[0696] 实例28:2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)丙酸(化合物28)

[0697] 步骤1:3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯

[0698] 

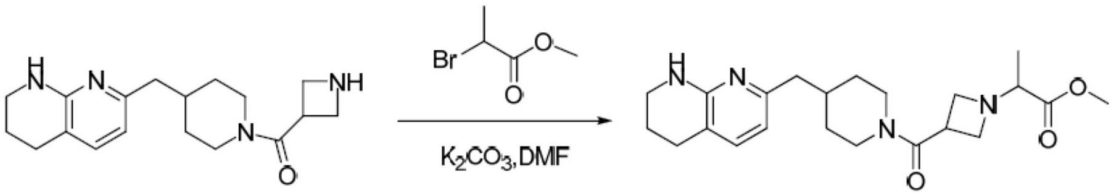
[0699] 将含于DMF(5mL)中的7-(哌啶-4-基甲基)-1,2,3,4-四氢-1,8-萘啶(100mg粗物质)、1-(叔丁氧羰基)氮杂环丁烷-3-甲酸(79mg,0.394mmol)、HATU(149mg,0.394mmol)和DIEA(127mg,0.986mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈黄色油的所需产物3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯(90mg)。产率61%(93%纯度,UV=214nm,ESI 415.2(M+H)$^+$)。

[0700] 步骤2:氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮

[0701] 

[0702] 在室温下,将3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-甲酸叔丁酯(90mg,0.217mmol)用含于DCM(3mL)中的TFA处理2小时。于真空中去除溶剂以得到呈黄色油的粗制氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮(70mg)。产率68.7%(100%纯度,UV=214nm,ESI 315.2(M+H)$^+$)。将粗产物直接由于下个步骤。

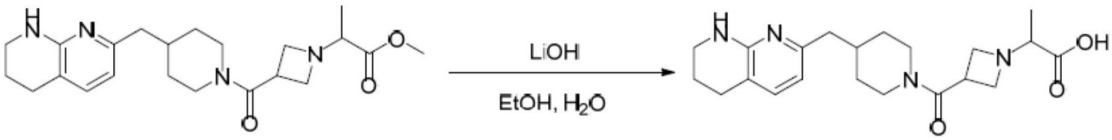
[0703] 步骤3:2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)丙酸甲酯

[0704] 

[0705] 将含于无水DMF(2mL)中的氮杂环丁烷-3-基(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲酮(70mg粗物质)、2-溴丙酸甲酯(55mg,0.333mmol)和K_2CO_3(92mg,0.667mmol)的混合物在室温下搅拌5小时。将反应过滤和于真空中浓缩。将残余物通过制备

型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)丙酸甲酯(49mg,29%产率)。(91%纯度,UV=254nm,ESI 401.2$(M+H)^+$)。

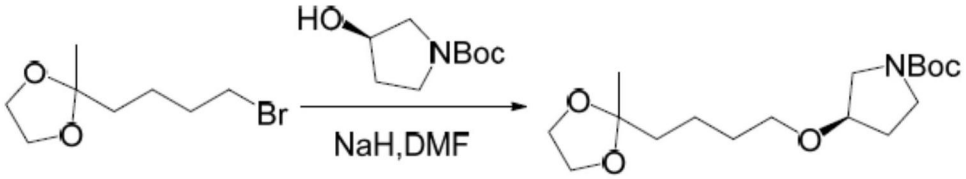
[0706] 步骤4:2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)丙酸(化合物28)

[0707] 

[0708] 在室温下,将2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)丙酸甲酯(49mg,0.12mmol)用含于EtOH(3mL)和H_2O(1mL)中的LiOH(10mg,0.25mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(33至65%MeCN)纯化以得到呈白色固体的化合物28(27mg,57%产率)。LC/MS A:100%纯度,UV=214nm,Rt=1.45min,ESI 387.3$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.15(d,J=7.3Hz,1H),6.36(d,J=7.3Hz,1H),4.48(d,J=13.2Hz,1H),4.33-4.04(m,4H),3.87(t,J=8.4Hz,1H),3.63(dd,J=20.6,11.3Hz,2H),3.43-3.36(m,2H),3.02(t,J=12.8Hz,1H),2.75-2.63(m,3H),2.47(d,J=7.1Hz,2H),1.97-1.87(m,3H),1.69(d,J=7.8Hz,2H),1.39(d,J=8.1Hz,3H),1.16(d,J=9.6Hz,2H)。

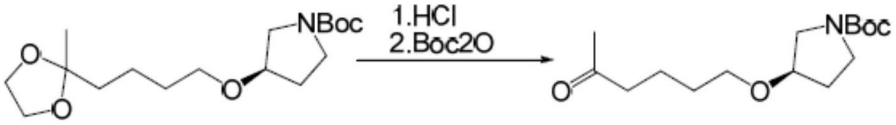
[0709] 实例29:制备2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(化合物129-E1和129-E2)

[0710] 步骤1:(R)-3-(4-(2-甲基-1,3-二氧戊环-2-基)丁氧基)吡咯烷-1-甲酸叔丁酯

[0711] 

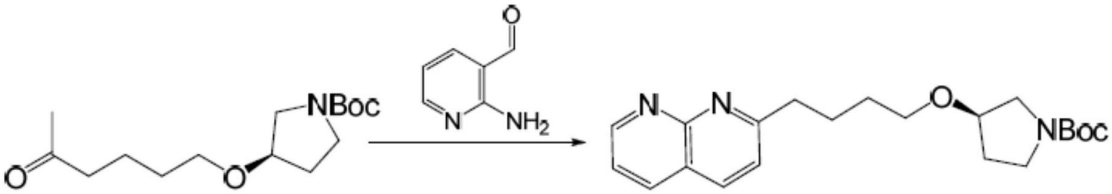
[0712] 在100℃下,将含于DMF(5mL)中的(R)-3-羟基吡咯烷-1-甲酸叔丁酯(1.09g,5.41mmol)、2-(4-溴丁基)-2-甲基-1,3-二氧戊环(1.2g,5.41mmol)和氢化钠(260mg,10.82mmol)的混合物搅拌6小时。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 10:1)纯化以得到呈无色油的所需产物(R)-3-(4-(2-甲基-1,3-二氧戊环-2-基)丁氧基)吡咯烷-1-甲酸叔丁酯(380mg)。产率21%(ESI 330.2$(M+H)^+$)。

[0713] 步骤2:(R)-3-(5-氧代基己氧基)吡咯烷-1-甲酸叔丁酯

[0714] 

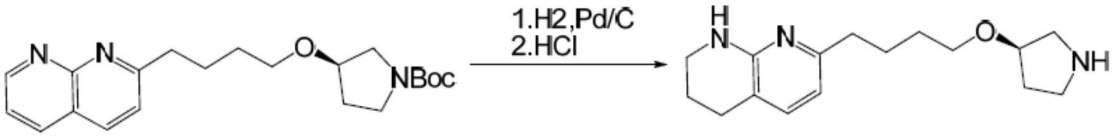
[0715] 在室温下,将(R)-3-(4-(2-甲基-1,3-二氧戊环-2-基)丁氧基)吡咯烷-1-甲酸叔丁酯(1.3g,3.95mmol)用HCl/二噁烷的溶液(4.0M,10mL)处理2小时。于真空中去除溶剂,和将残余物用丙酮(10mL)和H_2O(1mL)稀释。添加碳酸钾以调整pH至8至9,接着添加Boc_2O(1.24g,5.69mmol)。将反应在室温下搅拌3小时,然后过滤和在真空下浓缩。将残余物通过硅胶柱(石油醚:EtOAc 15:1)纯化以得到呈无色油的所需产物(R)-3-(5-氧代基己氧基)吡咯烷-1-甲酸叔丁酯(820mg)。产率73%(ESI 186$(M-100)^+$,230$(M-56)^+$)。

[0716] 步骤3:(R)-3-(4-(1,8-萘啶-2-基)丁氧基)吡咯烷-1-甲酸叔丁酯

[0717] 

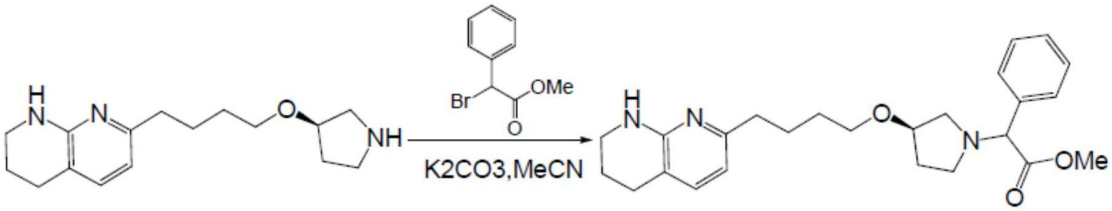
[0718] 在85℃下,将含于DMF(5mL)中的(R)-3-(5-氧代基己氧基)吡咯烷-1-甲酸叔丁酯(820mg,2.88mmol)、2-氨基烟碱醛(456mg,3.77mmol)和吡咯烷(265mg,3.77mmol)的混合物搅拌4小时。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 15:1)纯化以得到呈无色油的所需产物(R)-3-(4-(1,8-萘啶-2-基)丁氧基)吡咯烷-1-甲酸叔丁酯(750mg)。产率70%(ESI 372.2(M+H)$^+$)。

[0719] 步骤4:(R)-7-(4-(吡咯烷-3-基氧基)丁基)-1,2,3,4-四氢-1,8-萘啶

[0720] 

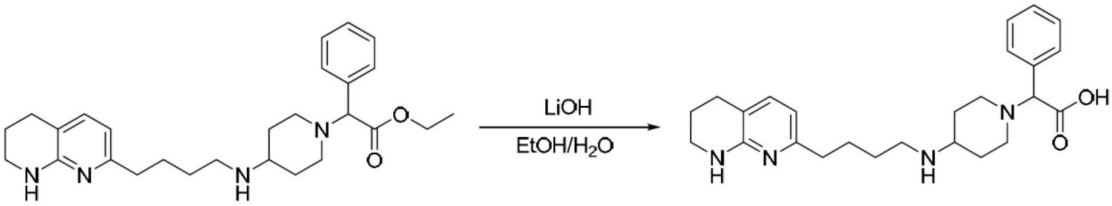
[0721] 在氢气下,在60℃下,将含于EtOAc(10mL)中的(R)-3-(4-(1,8-萘啶-2-基)丁氧基)吡咯烷-1-甲酸叔丁酯(750mg,2.02mmol)、Pd/C(10%,500mg)的混合物搅拌6小时。将反应过滤和于真空中浓缩。在室温下,将残余物用HCl/二噁烷的溶液(4.0M,4mL)处理2小时,和于真空中去除溶剂以得到呈白色固体的所需产物(R)-7-(4-(吡咯烷-3-基氧基)丁基)-1,2,3,4-四氢-1,8-萘啶(600mg)。产率96%(ESI 276.2(M+H)+)。

[0722] 步骤5:2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸甲酯

[0723] 

[0724] 将含于MeCN(3mL)中的(R)-7-(4-(吡咯烷-3-基氧基)丁基)-1,2,3,4-四氢-1,8-萘啶(200mg,0.576mmol)、2-溴-2-苯基乙酸甲酯(140mg,0.576mmol)和K_2CO_3(240mg,1.73mmol)的混合物在室温下搅拌过夜。于真空中去除溶剂,和将残余物直接由于下个步骤。(ESI 424.0(M+H)$^+$)。

[0725] 步骤6:2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(化合物129-E1和129-E2)

[0726] 

[0727] 在室温下,将2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸甲酯(180mg,0.426mmol)用含于EtOH(4mL)和H_2O(1mL)中的LiOH-H_2O(126mg,

3.0mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物129(105mg,60%产率)。将外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物129-E1(38.7mg)和化合物129-E2(37.5mg)。

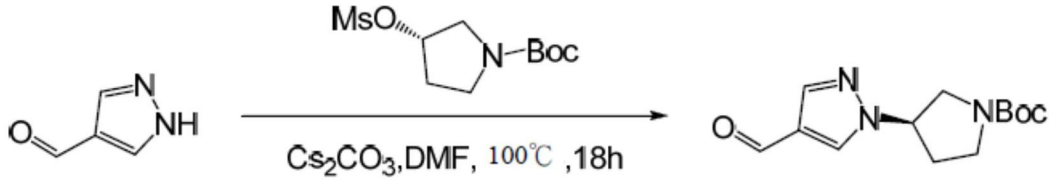
[0728] 化合物129-E1 LC/MS ESI 410(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.55-7.53(m,2H),7.43-7.41(m,3H),7.17(d,J=7.2Hz,1H),6.39(d,J=7.6Hz,1H),4.49(s,1H),4.18(s,1H),3.48-3.43(m,3H),3.39-3.36(t,J=11.5Hz,2H),3.13(d,J=10.8Hz,1H),3.01(m,1H),2.72-2.69(t,J=12.4Hz,2H),2.56-2.52(t,J=15.4Hz,2H),2.11(s,2H),1.89-1.86(m,2H),1.74-1.59(m,5H)。手性SFC A(40%MeOH):ee 89.9%,Rt=2.14min。

[0729] 化合物129-E2 LC/MS ESI 410(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.56-7.53(m,2H),7.42-7.41(m,3H),7.16(d,J=7.2Hz,1H),6.39(d,J=7.2Hz,1H),4.48(s,1H),4.17(m,1H),3.47-3.35(m,6H),3.17-3.12(m,2H),2.70(t,J=12.4Hz,2H),2.57-2.53(t,J=10.8Hz,2H),2.21-2.17(m,2H),1.90-1.84(m,2H),1.73-1.58(m,4H)。手性SFC A(40%MeOH):ee 94.4%,Rt=3.46min。

[0730] 实例30:制备2-苯基-2-((R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡唑-1-基)吡咯烷-1-基)乙酸(化合物130-E1和130-E2)

[0731] 步骤1:(R)-3-(4-甲醛基-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯

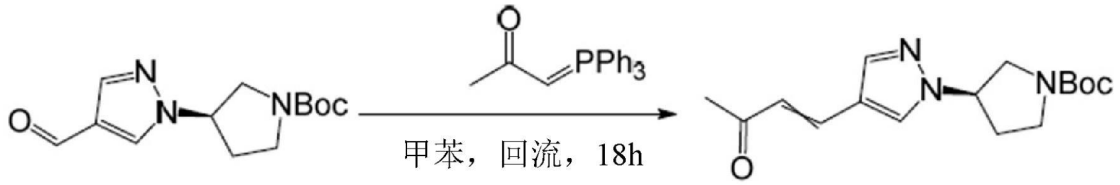
[0732]



[0733] 在100℃下,将含于DMF(30mL)中的1H-吡唑-4-甲醛(400mg,4.17mmol)、(S)-3-(甲基磺酰基氧基)吡咯烷-1-甲酸叔丁酯(1.21g,4.58mmol)和Cs_2CO_3(4.08g,12.51mmol)的混合物搅拌18小时。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物(R)-3-(4-甲醛基-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(1.0g)。产率91%(ESI 266.0(M+H)+)。

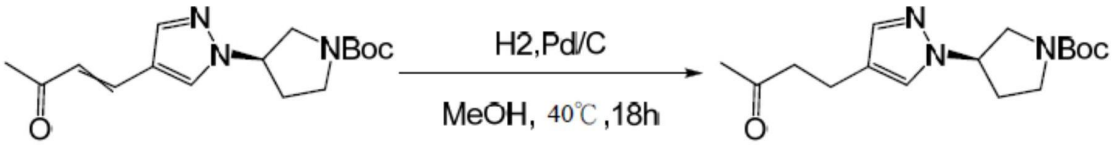
[0734] 步骤2:(R)-3-(4-(3-氧代基丁-1-烯基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯

[0735]



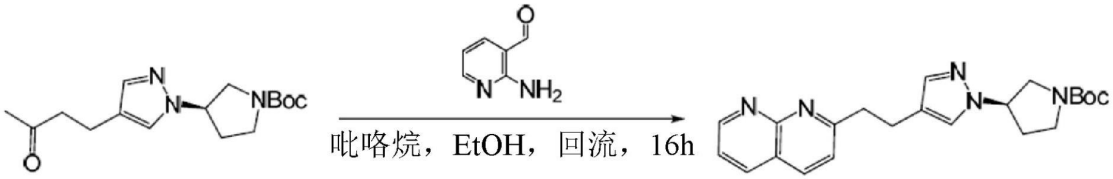
[0736] 在110℃下,将含于甲苯(40mL)中的(R)-3-(4-甲醛基-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(1g,3.77mmol)和1-(三苯基-亚磷基)丙-2-酮(1.2g,5.66mmol)的混合物搅拌18小时。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 1:1)纯化以得到呈无色油的所需产物(R)-3-(4-(3-氧代基丁-1-烯基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(920mg)。产率80%(ESI 306.0(M+H)+)。

[0737] 步骤3:(R)-3-(4-(3-氧代基丁基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯

[0738] 

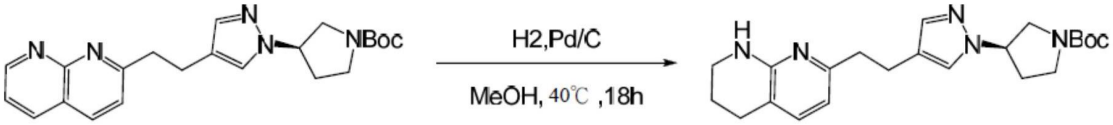
[0739] 在H_2下，在40℃下，将含于MeOH(20mL)中的(R)-3-(4-(3-氧代基丁-1-烯基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(920mg，3.02mmol)和10%Pd/C(184mg)的混合物搅拌18小时。将混合物过滤，和于真空中去除溶剂以得到呈无色油的所需产物(R)-3-(4-(3-氧代基丁基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(900mg)。产率97%(ESI 308.0(M+H)+)。

[0740] 步骤4：(R)-3-(4-(3-氧代基丁基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯

[0741] 

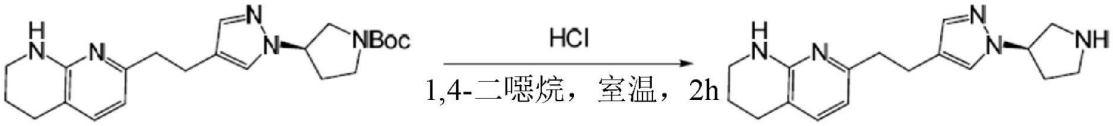
[0742] 在80℃下，将含于EtOH(30mL)中的((R)-3-(4-(3-氧代基丁基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(900mg，2.93mmol))、2-氨基烟碱醛(465mg，3.81mmol)和吡咯烷(270mg，3.81mmol)的混合物搅拌16小时。于真空中去除溶剂，和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈黄色油的所需产物(R)-3-(4-(3-氧代基丁基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(650mg)。产率56%(ESI 394.0(M+H)+)。

[0743] 步骤5：(R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯

[0744] 

[0745] 在40℃下，将含于MeOH(20mL)中的(R)-3-(4-(3-氧代基丁基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(650mg，1.65mmol)和10%Pd/C(130mg)的混合物搅拌15小时。将混合物过滤和于真空中去除溶剂以得到呈黄色油的所需产物(R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(610mg)。产率93%(ESI 398.0(M+H)+)。

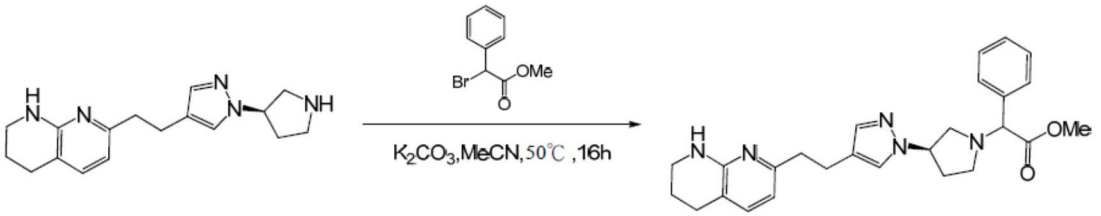
[0746] 步骤6：(R)-7-(2-(1-(吡咯烷-3-基)-1H-吡唑-4-基)乙基)-1,2,3,4-四氢-1,8-萘啶

[0747] 

[0748] 在25℃下，将(R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡唑-1-基)吡咯烷-1-甲酸叔丁酯(610mg，1.54mmol)用HCl(4M含于1,4-二噁烷中，3.9mL，15.4mmol)处理2小时。于真空中去除溶剂以得到呈黄色油的所需产物(R)-7-(2-(1-(吡咯烷-3-基)-1H-吡唑-4-基)乙基)-1,2,3,4-四氢-1,8-萘啶(450mg)。产率98%(ESI 298.0(M+H)+)。

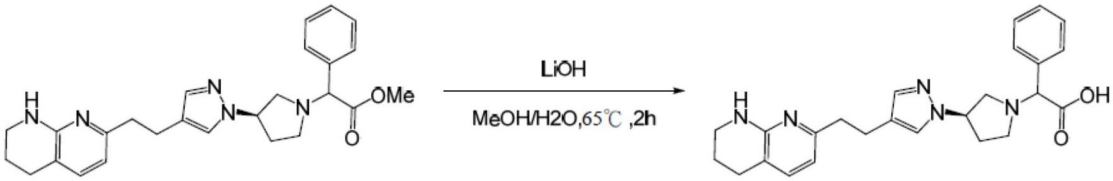
[0749] 步骤7：2-苯基-2-((R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡

唑-1-基)吡咯烷-1-基)乙酸甲酯

[0750] 

[0751] 在50℃下,将含于MeCN(20mL)中的(R)-7-(2-(1-(吡咯烷-3-基)-1H-吡唑-4-基)乙基)-1,2,3,4-四氢-1,8-萘啶(450mg,1.51mmol)、2-溴-2-苯基乙酸甲酯(415mg,1.81mmol)和K_2CO_3(625mg,4.53mmol)的混合物搅拌16小时。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 20:1)纯化以得到呈黄色油的所需产物2-苯基-2-((R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡唑-1-基)吡咯烷-1-基)乙酸甲酯(120mg)。产率19%(ESI 446.0(M+H)+)。

[0752] 步骤8:2-苯基-2-((R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡唑-1-基)吡咯烷-1-基)乙酸(化合物130-E1和130-E2)

[0753] 

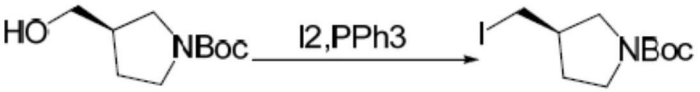
[0754] 在65℃下,将2-苯基-2-((R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1H-吡唑-1-基)吡咯烷-1-基)乙酸甲酯(120mg,0.27mmol)用含于MeOH(4mL)和H_2O(1mL)中的LiOH-H_2O(45.4mg,1.08mmol)处理2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物130(60mg,52%产率)。将外消旋产物通过制备型手性SFC B分离以得到呈白色固体的对映异构产物化合物130-E1(46mg)和化合物130-E2(27mg)。

[0755] 化合物130-E1 LC/MS ESI 432(M+H)+^{1}H NMR(400MHz,MeOD)δ7.59-7.56(m,3H),7.39-7.21(m,5H),6.39(d,J=7.3Hz,1H),4.97(s,1H),4.44(s,1H),3.44-3.36(m,4H),3.32-3.15(m,2H),2.81-2.79(m,4H),2.71(t,J=6.0Hz,2H),2.50-2.45(m,1H),2.25-2.20(m,1H),1.88-1.85(m,2H)。手性SFC B(40%MeOH):ee 100%,Rt=1.34min。

[0756] 化合物130-E2 LC/MS ESI 432(M+H)+^{1}H NMR(400MHz,MeOD)δ7.59-7.56(m,3H),7.39-7.21(m,5H),6.39(d,J=7.3Hz,1H),4.87(s,1H),4.07(s,1H),3.44-3.26(m,4H),2.92-2.51(m,8H),2.50-2.40(m,1H),2.20-2.10(m,1H),1.88-1.85(m,2H)。手性SFC B(40%MeOH):ee 99.5%,Rt=2.89min。

[0757] 实例31:制备2-苯基-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)乙酸(化合物131-E1和131-E2)

[0758] 步骤1:(R)-3-(碘甲基)吡咯烷-1-甲酸叔丁酯

[0759] 

[0760] 在0℃下,向含于DCM(50mL)中的三苯基膦(5.11g,19.5mmol)和1H-咪唑(1.33g,19.5mmol)的溶液中缓慢添加碘(4.95g,19.5mmol)。将反应在0℃下搅拌30分钟,和然后添

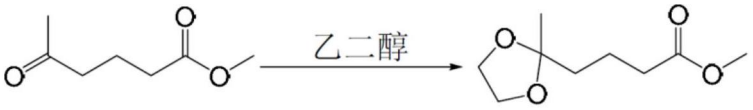
加含于DCM(10mL)中的(R)-3-(羟甲基)吡咯烷-1-甲酸叔丁酯的溶液。将反应在室温下搅拌过夜,然后用水(50mL)稀释和用DCM(30mL x 3)萃取。将合并的有机层经Na_2SO_4干燥,过滤和于真空中浓缩。将残余物通过硅胶柱(石油醚:EtOAc 10:1)纯化以得到呈无色油的所需产物(R)-3-(碘甲基)吡咯烷-1-甲酸叔丁酯(3.7g)。产率80%。(ESI 256(M+H-56)+)。

[0761] 步骤2:(R)-((1-(叔丁氧羰基)吡咯烷-3-基)甲基)三苯基鏻

[0762] 

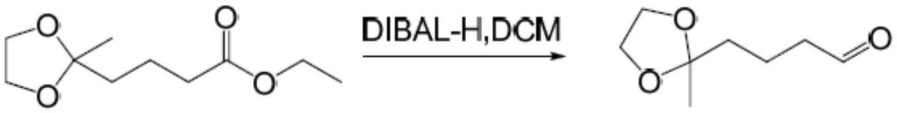
[0763] 将含于DMF(50mL)中的(R)-3-(碘甲基)吡咯烷-1-甲酸叔丁酯(3.7g,12mmol)和三苯基膦(4.1g,15.5mmol)的溶液在室温下搅拌过夜。于真空中去除溶剂,和将残余物通过硅胶柱(DCM:MeOH 10:1)纯化以得到粗产物。将乙醚(30mL)添加至所述粗产物,和将混合物在室温下搅拌30分钟。通过过滤收集固体和在真空下干燥以得到呈白色固体的所需产物(R)-((1-(叔丁氧羰基)吡咯烷-3-基)甲基)三苯基鏻(5.6g)。产率84%.(ESI N/A)。

[0764] 步骤3:4-(2-甲基-1,3-二氧戊环-2-基)丁酸乙酯

[0765] 

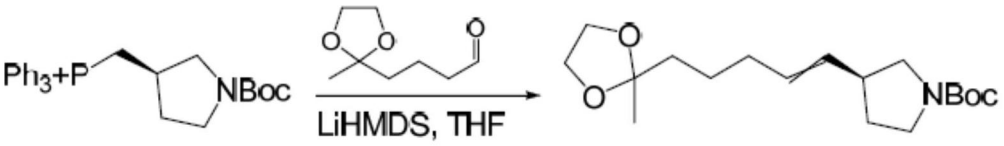
[0766] 利用迪恩-斯达克分离器(Dean-stark trap)将含于甲苯(50mL)中的5-氧代基己酸乙酯(2g,13.9mmol)、乙二醇(2.6g,42mmol)和对甲苯磺酸(478mg,2.78mmol)的溶液回流6小时。于真空中去除溶剂,和将残余物通过硅胶柱(石油醚:EtOAc 10:1)纯化以得到呈无色油的所需产物4-(2-甲基-1,3-二氧戊环-2-基)丁酸乙酯(1.4g,50%产率)。(ESI 203(M+H)+)。

[0767] 步骤4:4-(2-甲基-1,3-二氧戊环-2-基)丁醛

[0768] 

[0769] 在-78℃下,在Ar下,向含于DCM(10mL)中的4-(2-甲基-1,3-二氧戊环-2-基)丁酸乙酯(500mg,2.48mmol)的溶液中缓慢添加DIBAL-H(1M,3.7mL,3.7mmol)。将反应在-78℃下搅拌30分钟,然后用20mL水中止,升温至室温和用DCM(20mL x 3)萃取。将合并的有机层经硫酸钠干燥,过滤和在真空下浓缩。将残余物通过硅胶柱(石油醚:EtOAc 2:1)纯化以得到呈无色油的所需产物4-(2-甲基-1,3-二氧戊环-2-基)丁醛(220mg)。产率56%。(ESI 159(M+H)+)。

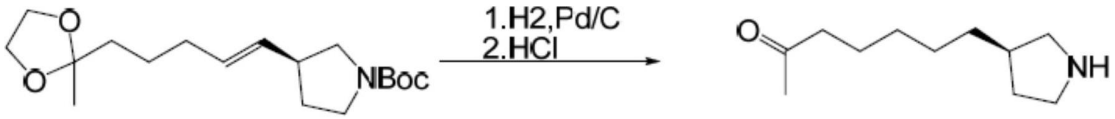
[0770] 步骤5:(S)-3-(5-(2-甲基-1,3-二氧戊环-2-基)戊-1-烯基)吡咯烷-1-甲酸叔丁酯

[0771] 

[0772] 在0℃下,在氮气下,向含于DCM(30mL)中的(R)-((1-(叔丁氧羰基)吡咯烷-3-基)甲基)三苯基鏻(2.0g,3.6mmol)的溶液中添加LiHMDS(1M,5.4mL,5.4mmol)。将混合物在0℃下搅拌30分钟,和然后添加4-(2-甲基-1,3-二氧戊环-2-基)丁醛(565mg,3.6mmol)。将反应

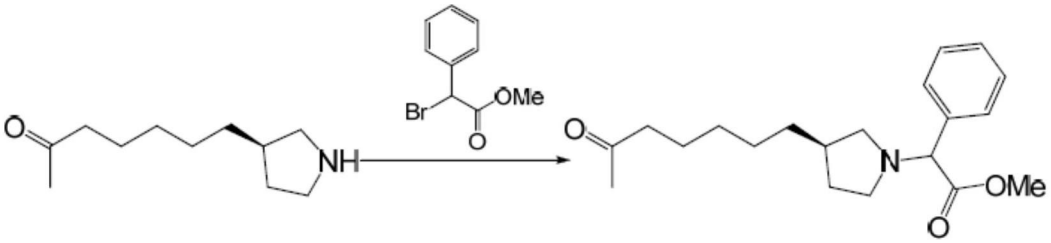
在室温下搅拌4小时，然后用MeOH(20mL)中止。于真空中去除溶剂，和将残余物通过硅胶柱(石油醚:EtOAc 3:1)纯化以得到呈黄色油的所需产物(S)-3-(5-(2-甲基-1,3-二氧戊环-2-基)戊-1-烯基)吡咯烷-1-甲酸叔丁酯(500mg)。产率43%。(ESI 226(M+H-100)+)。

[0773] 步骤6：(R)-7-(吡咯烷-3-基)庚-2-酮

[0774] 

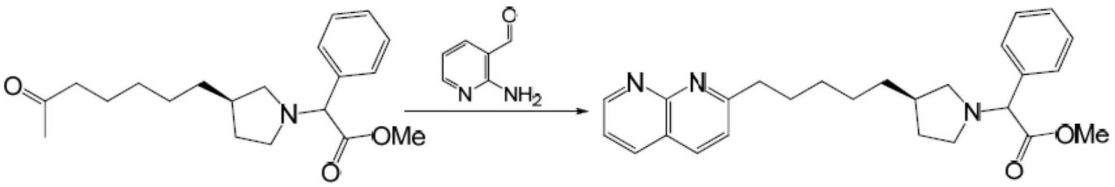
[0775] 在40℃下，在氢气下，将含于EtOAc(20mL)中的(S)-3-(5-(2-甲基-1,3-二氧戊环-2-基)戊-1-烯基)吡咯烷-1-甲酸叔丁酯(440mg，1.35mmol)和Pd/C(10%，40mg)的混合物搅拌过夜。将反应过滤和于真空中浓缩。将残余物用5mL HCl的1,4-二噁烷溶液(4M)处理。将混合物在室温下搅拌2小时，然后于真空中浓缩以得到呈黄色油的所需产物(R)-7-(吡咯烷-3-基)庚-2-酮。(220mg)。产率89%。(ESI 184(M+H)+)。

[0776] 步骤7：2-((R)-3-(6-氧代基庚基)吡咯烷-1-基)-2-苯基乙酸甲酯

[0777] 

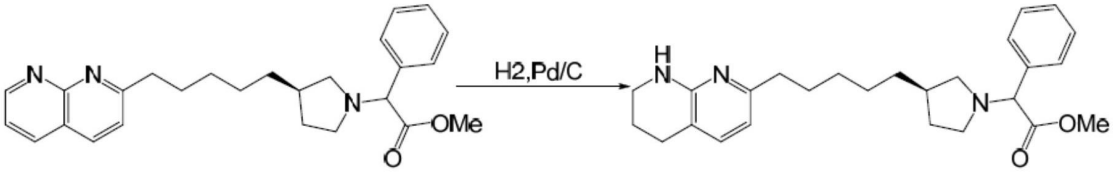
[0778] 在40℃下，将含于MeCN(10mL)中的(R)-7-(吡咯烷-3-基)庚-2-酮(210mg，1.15mmol)、2-溴-2-苯基乙酸甲酯(315mg，1.4mmol)和K_2CO_3(476mg，3.45mmol)的混合物搅拌过夜。将反应过滤和于真空中浓缩，和将残余物通过硅胶柱(DCM:MeOH＝30:1)纯化以得到呈黄色油的所需产物2-((R)-3-(6-氧代基庚基)吡咯烷-1-基)-2-苯基乙酸甲酯(260mg)。产率68%。(ESI 331(M+H)+)。

[0779] 步骤8：2-((R)-3-(5-(1,8-萘啶-2-基)戊基)吡咯烷-1-基)-2-苯基乙酸甲酯

[0780] 

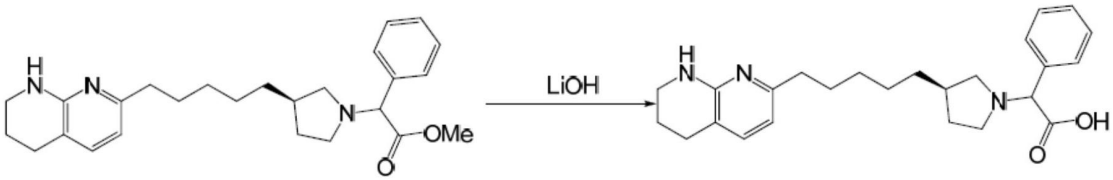
[0781] 向含于EtOH(10mL)中的2-((R)-3-(6-氧代基庚基)吡咯烷-1-基)-2-苯基乙酸甲酯(260mg，0.78mmol)的溶液中添加2-氨基烟碱醛(144mg，1.18mmol)和吡咯烷(28mg，0.39mmol)。将反应加热至回流过夜，然后于真空中浓缩，和将残余物通过硅胶柱(DCM:MeOH＝20:1)纯化以得到呈黄色油的所需产物2-((R)-3-(5-(1,8-萘啶-2-基)戊基)吡咯烷-1-基)-2-苯基乙酸甲酯(260mg)。产率78%。(ESI 418(M+H)+)。

[0782] 步骤9：2-苯基-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)乙酸甲酯

[0783] 

[0784] 在40℃下，在氢气下，将含于EtOAc(10mL)中的2-((R)-3-(5-(1,8-萘啶-2-基)戊基)吡咯烷-1-基)-2-苯基乙酸甲酯(260mg，0.62mmol)和Pd/C(10%，30mg)的混合物搅拌过夜。将反应过滤和于真空中浓缩以得到呈黄色油的所需产物2-苯基-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)乙酸甲酯(220mg)。产率84%。(ESI 422(M+H)+)。

[0785] 步骤10：2-苯基-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)乙酸(化合物131-E1和131-E2)

[0786] 

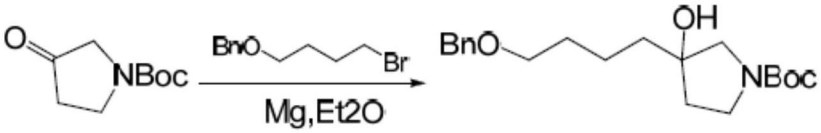
[0787] 在室温下，将2-苯基-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)乙酸甲酯(200mg，0.49mmol)用含于MeOH(10mL)和H_2O(2mL)中的LiOH-H_2O(83mg，1.97mmol)处理2小时。于真空中去除溶剂，和将残余物通过制备型-HPLC纯化以得到呈白色固体的化合物131(120mg，62%产率)。将外消旋产物通过制备型手性SFC A分离以得到呈白色固体的对映异构产物化合物131-E1(35mg)和化合物131-E2(39mg)。

[0788] 化合物131-E1 LC/MS ESI 408(M+H)+ ^{1}H NMR(400MHz，MeOD)δ7.58-7.55(m,2H)，7.44-7.41(m,3H)，7.12(d,J=7.2Hz,1H)，6.35(d,J=7.2Hz,1H)，4.49(s,1H)，3.71-3.62(m,1H)，3.41-3.36(m,3H)，3.02-2.95(m,1H)，2.72-2.66(m,3H)，2.50(t,J=7.2Hz,2H)，2.41-2.11(m,2H)，1.92-1.84(m,2H)，1.69-1.25(m,9H)。手性SFC A(40%MeOH)：ee 100%，Rt=2.04min。

[0789] 化合物131-E2 LC/MS ESI 408(M+H)+ ^{1}H NMR(400MHz，MeOD)δ7.47-7.44(m,2H)，7.34-7.31(m,3H)，7.00(d,J=7.2Hz,1H)，6.22(d,J=7.2Hz,1H)，4.39(s,1H)，3.39-3.26(m,3H)，2.98-2.78(m,3H)，2.58(t,J=6.4Hz,2H)，2.38(t,J=7.6Hz,2H)，2.28-2.01(m,2H)，1.78-1.74(m,2H)，1.60-1.15(m,9H)。手性SFC A(40%MeOH)：ee 100%，Rt=3.86min。

[0790] 实例32：制备2-(3-氟-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)-2-苯基乙酸(化合物132-E1和132-E2)

[0791] 步骤1：3-(4-(苄氧基)丁基)-3-羟基吡咯烷-1-甲酸叔丁酯

[0792] 

[0793] 向含于Et_2O(20mL)中的((4-溴丁氧基)甲基)苯(9.45g，38.87mmol)和Mg(1.89g，77.74mmol)的混合物中添加I_2(202mg，1.09mmol)。将反应混合物在40℃下搅拌1小时。于冷却至室温后，在5℃下，将混合物添加至含于30mL Et_2O中的3-氧代基吡咯烷-1-甲酸叔丁酯(2.4g，12.96mmol)的溶液中。将反应在室温下搅拌过夜，然后用NH_4Cl水溶液(10mL)中止和

用EtOAc(30mL x 3)萃取。将合并的有机层经硫酸钠干燥,过滤和于真空中浓缩。将残余物通过硅胶柱(石油醚:EtOAc 5:1至2:1)纯化以得到呈黄色油的所需产物3-(4-(苄氧基)丁基)-3-羟基吡咯烷-1-甲酸叔丁酯(1.7g)。产率38%(ESI 294(M+H-56)$^+$)。

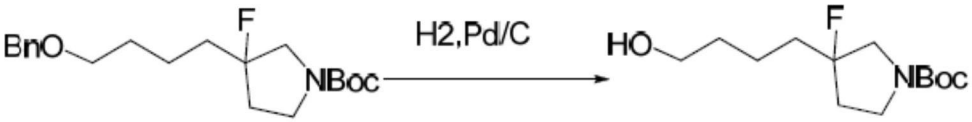
[0794] 步骤2:3-(4-(苄氧基)丁基)-3-氟吡咯烷-1-甲酸叔丁酯

[0795] 

[0796] 在40℃下,将含于DCM(30mL)中的3-(4-(苄氧基)丁基)-3-羟基吡咯烷-1-甲酸叔丁酯(1.7g,4.86mmol)和BAST(10.76g,48.6mmol)的混合物搅拌24小时。将反应用MeOH(2mL)稀释,用水(20mL)洗涤,经硫酸钠干燥,过滤和于真空中浓缩。将残余物通过硅胶柱(石油醚:EtOAc 20:1至10:1)纯化以得到呈浅黄色油的所需产物3-(4-(苄氧基)丁基)-3-氟吡咯烷-1-甲酸叔丁酯(1.1g)。产率64%(ESI 296

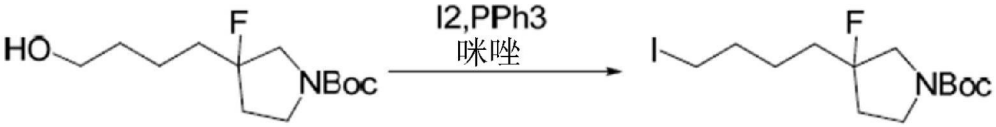
[0797] (M+H-56)$^+$)。

[0798] 步骤3:3-氟-3-(4-羟丁基)吡咯烷-1-甲酸叔丁酯

[0799] 

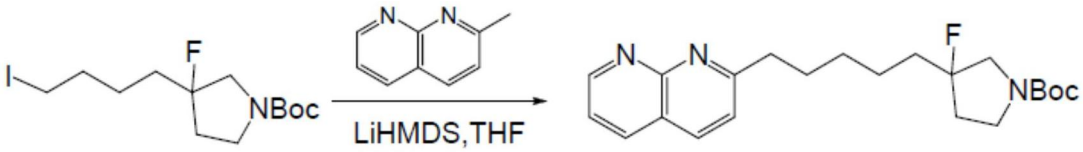
[0800] 在氢气下,在45℃下,将含于EtOAc(100mL)中的3-(4-(苄氧基)丁基)-3-氟吡咯烷-1-甲酸叔丁酯(1.1g,3.13mmol)和Pd/C(5%,1.1g)的混合物搅拌过夜。将混合物过滤和于真空中浓缩以得到呈浅黄色油的所需产物3-氟-3-(4-羟丁基)吡咯烷-1-甲酸叔丁酯(780mg)。产率95%(ESI 206(M+H-56)$^+$)。

[0801] 步骤4:3-氟-3-(4-碘丁基)吡咯烷-1-甲酸叔丁酯

[0802] 

[0803] 在5℃下,向含于DCM(40mL)中的三苯基膦(1.58g,6.04mmol)和咪唑(411mg,6.04mmol)的溶液中添加I_2(835mg,3.29mmol)。将反应混合物在5℃下搅拌15分钟,和然后添加含于DCM(15mL)中的3-氟-3-(4-羟丁基)吡咯烷-1-甲酸叔丁酯(780mg,2.99mmol)的溶液。将反应混合物在5℃下搅拌1小时,然后在15℃下,于真空中浓缩,和将残余物通过硅胶柱(石油醚:EtOAc 20:1至10:1)纯化以得到呈浅黄色油的所需产物3-氟-3-(4-碘丁基)吡咯烷-1-甲酸叔丁酯(700mg)。产率63%(ESI 316(M+H-56)$^+$)。

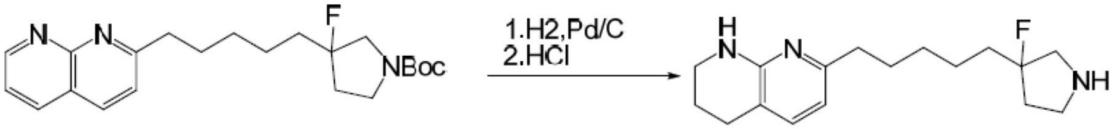
[0804] 步骤5:3-(5-(1,8-萘啶-2-基)戊基)-3-氟吡咯烷-1-甲酸叔丁酯

[0805] 

[0806] 在0℃下,向含于THF(12mL)中的3-氟-3-(4-碘丁基)吡咯烷-1-甲酸叔丁酯(700mg,1.88mmol)和2-甲基-1,8-萘啶(407mg,2.82mmol)的溶液中添加LiHMDS(2.82mL,1M,2.82mmol)。将反应混合物在0℃下搅拌3小时,然后用饱和氯化铵溶液(6mL)中止,用水(15mL)稀释和用EtOAc(30mL x 2)萃取。将合并的有机层经硫酸钠干燥,过滤和于真空中浓

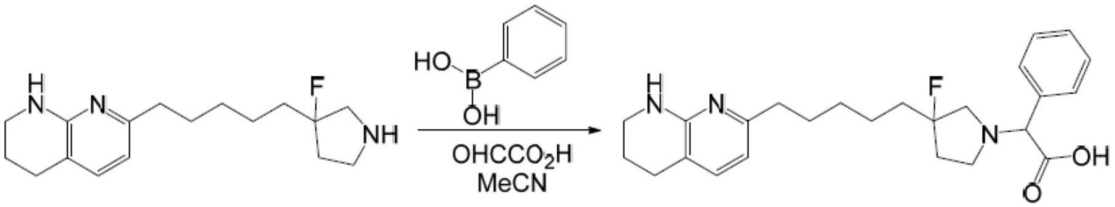
缩。将残余物通过制备型-TLC纯化以得到呈浅黄色固体的所需产物3-(5-(1,8-萘啶-2-基)戊基)-3-氟吡咯烷-1-甲酸叔丁酯(350mg)。产率48%(ESI 388(M+H)$^+$)。

[0807] 步骤6:7-(5-(3-氟吡咯烷-3-基)戊基)-1,2,3,4-四氢-1,8-萘啶

[0808] 

[0809] 在氢气下,在45℃下,将含于EtOAc(20mL)中的3-(5-(1,8-萘啶-2-基)戊基)-3-氟吡咯烷-1-甲酸叔丁酯(200mg,0.516mmol)和Pd/C(5%,200mg)的混合物搅拌过夜。将反应混合物过滤和于真空中浓缩。在室温下,向残余物中添加1,4-二噁烷(2mL)和HCl/二噁烷(2mL,4M)。将反应混合物在室温下搅拌3小时,然后于真空中浓缩以得到呈浅黄色固体的所需产物7-(5-(3-氟吡咯烷-3-基)戊基)-1,2,3,4-四氢-1,8-萘啶(140mg)。产率93%(ESI 292(M+H)$^+$)。

[0810] 步骤7:2-(3-氟-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)-2-苯基乙酸(化合物132-E1和132-E2)

[0811] 

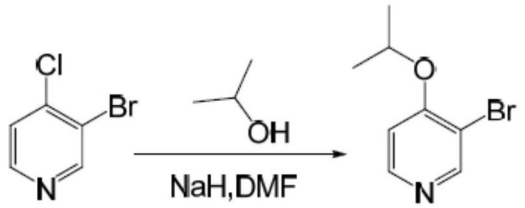
[0812] 在50℃下,将含于MeCN(1.5mL)中的7-(5-(3-氟吡咯烷-3-基)戊基)-1,2,3,4-四氢-1,8-萘啶(140mg,0.48mmol)、2-氧代基乙酸(76.5mg,0.62mmol)和苯基二羟基硼酸(75.6mg,0.62mmol)的混合物加热2小时。于真空中去除溶剂,和将残余物通过制备型-HPLC A纯化以得到呈白色固体的化合物132(90mg,44%产率)。将外消旋产物通过制备型手性SFC A分离以得到呈白色固体的化合物132-E1(41mg)和化合物132-E2(36mg)。

[0813] 化合物132-E1 LC/MS ESI 426(M+H)+^{1}H NMR(500MHz,MeOD)δ7.47-7.45(m,2H),7.31-7.29(m,3H),7.08(d,J=7.5Hz,1H),6.27(d,J=7.5Hz,1H),4.31(d,1H),3.43-3.27(m,4H),3.08-2.90(m,2H),2.60(t,J=6.0Hz,2H),2.42(t,J=8.5Hz,2H),2.11-1.93(m,2H),1.80-1.63(m,4H),1.57-1.49(m,2H),1.39-1.19(m,4H)。手性SFC A(40%MeOH):ee 100%,Rt=2.45min。

[0814] 化合物132-E2 LC/MS ESI 426(M+H)+^{1}H NMR(500MHz,MeOD)δ7.59-7.57(m,2H),7.42-7.38(m,3H),7.22(d,J=8.0Hz,1H),6.40(d,J=7.5Hz,1H),4.33(d,1H),3.46-3.30(m,4H),3.16-2.93(m,2H),2.72(t,J=6.0Hz,2H),2.55(t,J=7.5Hz,2H),2.25-2.05(m,2H),1.91-1.87(m,2H),1.85-1.73(m,2H),1.68-1.62(m,2H),1.48-1.31(m,4H)。手性SFC A(40%MeOH):ee 98%,Rt=3.92、4.42min。

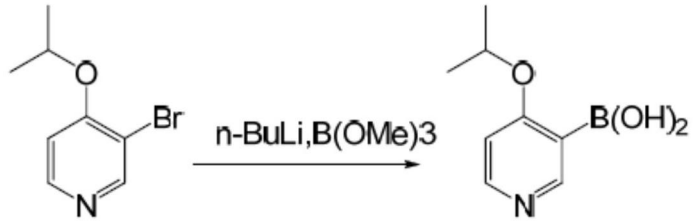
[0815] 实例33:制备2-(4-异丙氧基吡啶-3-基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(化合物133)

[0816] 步骤1:3-溴-4-异丙氧基吡啶

[0817] 

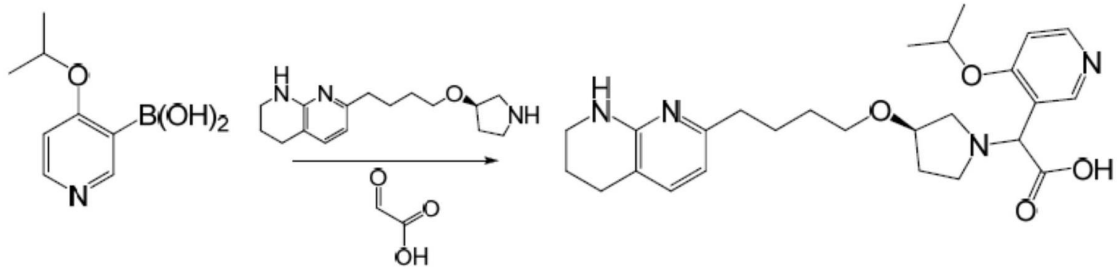
[0818] 在0℃下，向含于DMF(20mL)中的i-PrOH(1.87g，31.2mmol)的溶液中添加NaH(60%，1.25g，31.2mmol)。将混合物在室温下搅拌1小时，和添加3-溴-4-氯吡啶(2g，10.4mmol)。将反应在80℃下搅拌过夜，然后冷却至室温，用H_2O(20mL)稀释和用EtOAc(20mLx 3)萃取。将合并的有机层经硫酸钠干燥，过滤和于真空中浓缩，和将残余物通过硅胶柱(石油醚:EtOAc 5:1)纯化以得到呈无色油的所需产物3-溴-4-异丙氧基吡啶(1.7g)。产率76%(ESI 216.0$(M+H)^+$)。

[0819] 步骤2:4-异丙氧基吡啶-3-基二羟基硼酸

[0820] 

[0821] 在Ar下，在-78℃下，向含于无水THF(20mL)中的3-溴-4-异丙氧基吡啶(1g，4.63mmol)的溶液中添加n-BuLi(2.5M含于己烷中，2.8mL)。将反应在-78℃下搅拌1小时，然后添加硼酸三甲酯(722mg，6.95mmol)。将反应在室温下搅拌过夜，然后用MeOH(5mL)中止和于真空中浓缩，和将残余物直接用于下个步骤。

[0822] 步骤3:2-(4-异丙氧基吡啶-3-基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(化合物133)

[0823] 

[0824] 将以上残余物用MeCN(10mL)稀释，添加(R)-7-(4-(吡咯烷-3-基氧基)丁基)-1,2,3,4-四氢-1,8-萘啶(150mg，0.54mmol)和乙醛酸(50%含于水中，161mg，1.08mmol)。将反应在回流下搅拌15小时。于真空中去除溶剂，和将残余物通过制备型-HPLC A(30至65%MeCN)纯化以得到呈白色固体的化合物133(20mg)。

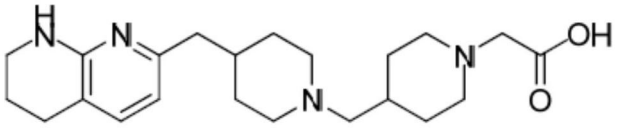
[0825] 化合物133 LC/MS ESI 469$(M+H)^+$ ^{1}H NMR(400MHz，MeOD)δ8.56(s，1H)，8.40(d，J=6Hz，1H)，7.19-7.14(m，2H)，6.38(d，J=7.2Hz，1H)，4.89-4.86(m，2H)，4.25-4.19(m，1H)，3.48-3.30(m，8H)，2.71(t，J=6.4Hz，2H)，2.55(t，J=7.6Hz，2H)，2.25-1.88(m，4H)，1.71-1.38(m，10H)。

[0826] 其它实例

[0827] 使用基于制备化合物1至28和129至133所使用方法的一般程序，制备化合物29至

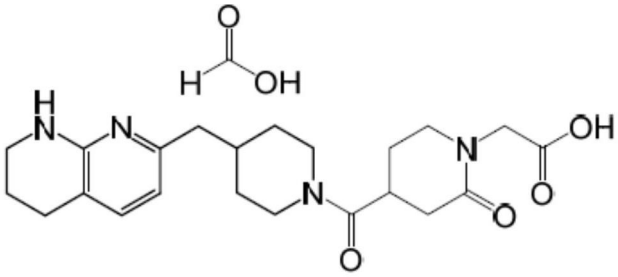
128和134至201。

[0828] 2-(4-((4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲基)哌啶-1-基)乙酸(化合物29)

[0829] 

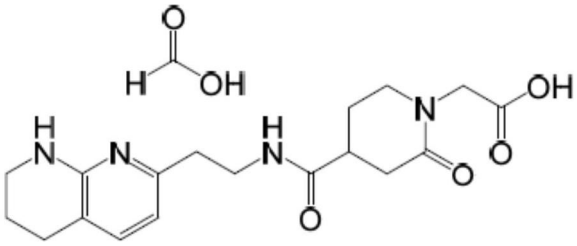
[0830] 化合物29 LC/MS A:100%纯度,UV=214nm,Rt=1.18min,ESI 387.2(M+H)$^{+}$。^{1}H NMR(500MHz,MeOD)δ7.13(d,J=7.3Hz,1H),6.34(d,J=7.3Hz,1H),3.50-3.48(m,4H),3.38(dd,J=14.9,9.3Hz,2H),2.93(d,J=11.5Hz,2H),2.85(t,J=11.8Hz,2H),2.71(t,J=6.2Hz,2H),2.45(d,J=7.0Hz,2H),2.28(d,J=7.0Hz,2H),2.01-1.98(m,4H),1.65-1.62(m,3H),1.73-1.56(m,3H),1.52-1.40(m,2H),1.33(dd,J=22.6,10.5Hz,2H)。

[0831] 2-(2-氧代基-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)哌啶-1-基)乙酸甲酸盐(化合物30)

[0832] 

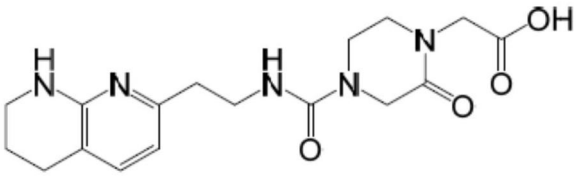
[0833] 化合物30LC/MS D:100%纯度,UV=214nm,Rt=1.427min,ESI415.1(M+H)+。^{1}H NMR(400MHz,DMSO-d6)δ8.18(0.73H,HCOOH),7.03(d,J=7.6Hz,1H),6.41(s,1H),6.23(d,J=7.2Hz,1H),4.36-4.33(m,1H),4.08-4.03(m,1H),3.92-3.78(m,2H),3.39-3.15(m,5H),2.98-2.92(m,1H),2.62-2.59(m,2H),2.50-2.23(m,5H),1.88-1.85(m,2H),1.76-1.72(m,3H),1.68-1.59(m,2H),1.13-0.96(m,2H)。

[0834] 2-(2-氧代基-4-((2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)氨甲酰基)哌啶-1-基)乙酸甲酸盐(化合物31)

[0835] 

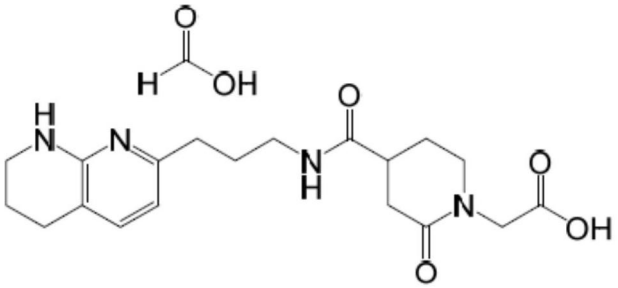
[0836] 化合物31 LC/MS D:100%纯度,UV=214nm,Rt=1.290min,ESI361.0(M+H)+。^{1}H NMR(400MHz,DMSO-d6)δ8.18(1H,HCOOH),7.98-7.95(m,1H),7.04(d,J=7.2Hz,1H),6.41(s,1H),6.24(d,J=7.6Hz,1H),4.12-4.07(m,1H),3.78-3.74(m,1H),3.33-3.24(m,5H),2.62-2.53(m,6H),2.32-2.29(m,2H),1.90-1.87(m,1H),1.77-1.72(m,3H)。

[0837] 2-(2-氧代基-4-((2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)氨甲酰基)哌嗪-1-基)乙酸(化合物32)

[0838] 

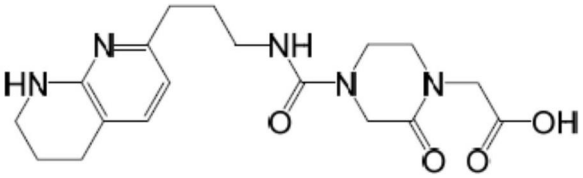
[0839] 化合物32 LC/MS D:97%纯度,UV=214nm,Rt=0.838min,ESI362.1(M+H)+。^{1}H NMR(400MHz,DMSO-d6)δ7.06(d,J=7.2Hz,1H),6.72(t,J=5.2Hz,1H),6.49(s,1H),6.26(d,J=7.2Hz,1H),4.02(s,2H),3.93(s,2H),3.56-3.53(m,2H),3.36-3.33(m,2H),3.29-3.24(m,4H),2.62-2.57(m,4H),1.78-1.72(m,2H)。

[0840] 2-(2-氧代基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸化合物甲酸盐(化合物33)

[0841] 

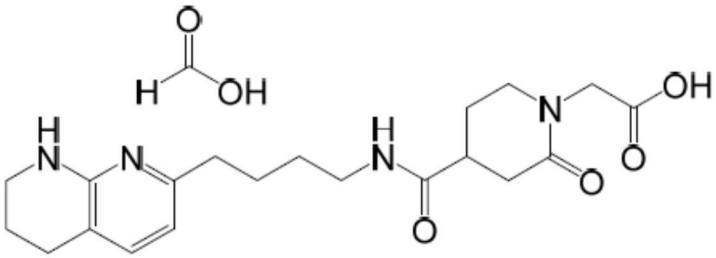
[0842] 化合物33 LC/MS D:100%纯度,UV=214nm,Rt=1.353min,ESI375.1(M+H)+。^{1}H NMR(400MHz,DMSO-d6)δ8.14(0.27H,HCOOH),7.97-7.94(m,1H),7.37(s,1H),7.26(d,J=6.8Hz,1H),6.40(d,J=7.2Hz,1H),3.97-3.86(m,2H),3.39-3.29(m,4H),3.10-3.04(m,2H),2.66-2.63(m,3H),2.50-2.48(m,2H),2.38-2.34(m,2H),1.90-1.68(m,6H)。

[0843] 2-(2-氧代基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌嗪-1-基)乙酸(化合物34)

[0844] 

[0845] 化合物34 LC/MS B:96%纯度,UV=214nm,Rt=1.285min,ESI376.3(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.48(d,J=7.6Hz,1H),6.53(d,J=7.6Hz,1H),4.12(s,2H),3.94(s,2H),3.76-3.74(m,2H),3.52-3.49(m,2H),3.46-3.43(m,2H),3.30-3.28(m,2H),2.79-2.75(m,2H),2.70-2.66(m,2H),1.93-1.90(m,2H),1.79-1.75(m,2H)。

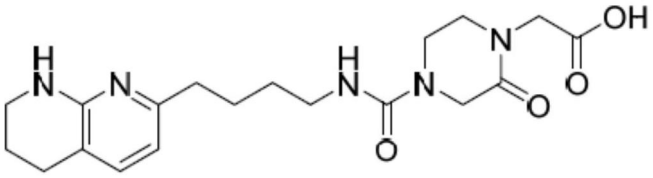
[0846] 2-(2-氧代基-4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)哌啶-1-基)乙酸(化合物35)

[0847] 

[0848] 化合物35 LC/MS C:98%纯度,UV=214nm,Rt=1.378min,ESI389.1(M+H)+。^{1}H

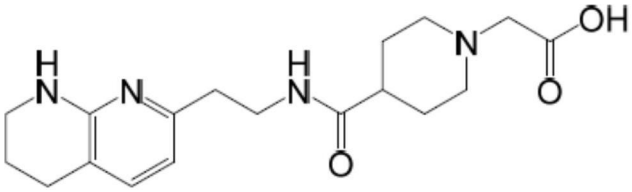
NMR(400MHz,DMSO-d6)δ8.18(0.37H,HCOOH),7.89-7.86(m,1H),7.07(d,J=7.2Hz,1H),6.87(s,1H),6.27(d,J=7.2Hz,1H),4.01-3.97(m,1H),3.85-3.80(m,1H),3.32-3.29(m,2H),3.27-3.20(m,2H),3.08-3.03(m,2H),2.64-2.59(m,3H),2.46-2.38(m,2H),2.38-2.31(m,2H),1.91-1.87(m,1H),1.80-1.73(m,3H),1.58-1.53(m,2H),1.43-1.37(m,2H)。

[0849] 2-(2-氧代基-4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)哌嗪-1-基)乙酸(化合物36)

[0850] 

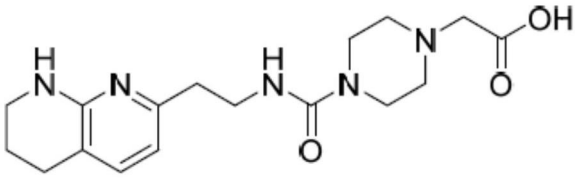
[0851] 化合物36 LC/MS D:100%纯度,UV=214nm,Rt=0.999min,ESI390.3(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.59(d,J=7.2Hz,1H),6.63(d,J=7.6Hz,1H),4.17(s,2H),4.08(s,2H),3.71-3.68(m,2H),3.52-3.48(m,4H),3.24-3.20(m,2H),2.84-2.80(m,2H),2.75-2.71(m,2H),1.97-1.94(m,2H),1.70(d,J=7.6Hz,2H),1.58(d,J=7.6Hz,2H)。

[0852] 2-(4-((2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)氨甲酰基)哌啶-1-基)乙酸(化合物37)

[0853] 

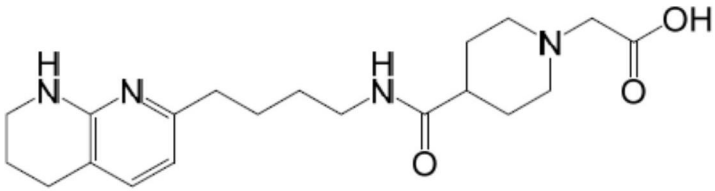
[0854] 化合物37 LC/MS A:96.8%纯度,UV=214nm,Rt=1.31min,ESI 347.2(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.17(d,J=7.2Hz,1H),6.38(d,J=7.2Hz,1H),3.62-3.57(m,4H),3.48-3.36(m,4H),3.03-2.96(m,2H),2.73-2.69(m,4H),2.50-2.44(m,1H),2.02-1.86(m,6H)。

[0855] 2-(4-((2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)氨甲酰基)哌嗪-1-基)乙酸(化合物38)

[0856] 

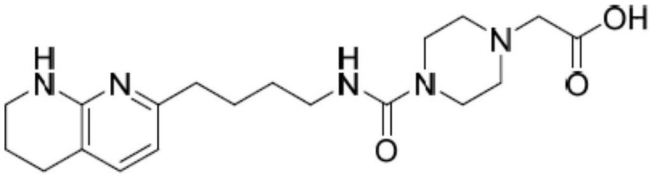
[0857] 化合物38 LC/MS A:99%纯度,UV=214nm,Rt=1.28min,ESI 348.3(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.25(d,J=7.3Hz,1H),6.44(d,J=7.3Hz,1H),3.59-3.57(m,4H),3.49-3.38(m,6H),3.04-3.03(m,4H),2.77-2.74(m,4H),1.93-1.88(m,2H)。

[0858] 2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)哌啶-1-基)乙酸(化合物39)

[0859] 

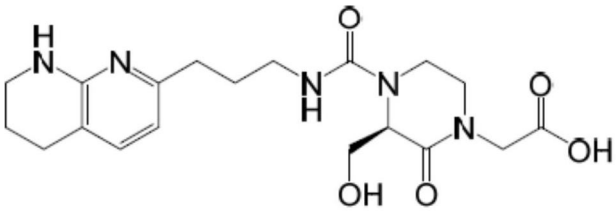
[0860] 化合物39 LC/MS A:97.4%纯度,UV=214nm,Rt=1.71min,ESI 375.3(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.03(d,J=7.6Hz,1H),6.26(d,J=7.6Hz,1H),3.52-3.45(m,4H),3.27(t,J=5.2Hz,2H),3.09(t,J=6.4Hz,2H),2.92-2.85(m,2H),2.59(t,J=6.4Hz,2H),2.44-2.35(m,3H),1.92-1.74(m,6H),1.56-1.39(m,4H)。

[0861] 2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)哌嗪-1-基)乙酸(化合物40)

[0862] 

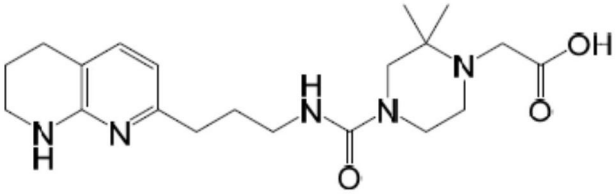
[0863] 化合物40LC/MS B:100%纯度,UV=214nm,Rt=0.82min,ESI376.0(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.32(d,J=7.3Hz,1H),6.45(d,J=7.3Hz,1H),3.54(t,J=4.Hz,4H),3.42(t,J=5.6Hz,2H),3.37(s,2H),3.21(t,J=6.6Hz,2H),2.98(t,J=5.2Hz,2H),2.75(t,J=6.2Hz,2H),2.61(t,J=7.6Hz,2H),1.98-1.83(m,2H),1.75-1.48(m,4H)。

[0864] (R)-2-(3-(羟甲基)-2-氧代基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌嗪-1-基)乙酸(化合物41)

[0865] 

[0866] 化合物41 LC/MS B:100%纯度,UV=214nm,Rt=1.01min,ESI406.2(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.35(d,J=7.2Hz,1H),6.42(d,J=7.2Hz,1H),4.50(brs,1H),4.40(m,1H),4.00-3.95(m,2H),3.83-3.79(m,1H),3.66-3.51(m,2H),3.36-3.30(m,4H),3.15-3.07(m,2H),2.68-2.49(m,4H),1.85-1.63(m,4H)。

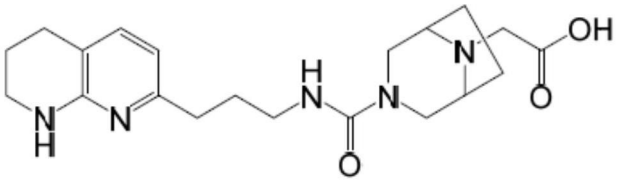
[0867] 2-(2,2-二甲基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌嗪-1-基)乙酸(化合物42)

[0868] 

[0869] 化合物42 LC/MS B:100%纯度,UV=214nm,Rt=1.12min,ESI390.2(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.24(d,J=7.6Hz,1H),6.44(d,J=7.6Hz,1H),3.67-3.65(m,2H),3.50(s,2H),3.46(s,2H),3.43-3.40(m,2H),3.24-3.19(m,4H),2.75-2.72(m,2H),2.62-

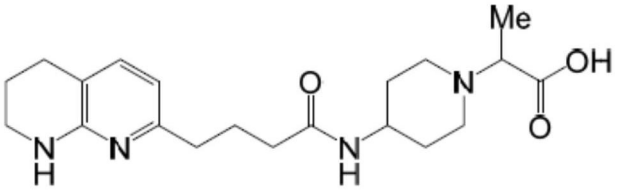
2.57(m,2H),1.92-1.83(m,4H),1.30(s,6H)。

[0870] 2-(3-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)-3,8-二氮杂双环[3.2.1]辛烷-8-基)乙酸(化合物43)

[0871] 

[0872] 化合物43 LC/MS A:100%纯度,UV=214nm,Rt=1.12min,ESI 387(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.19(d,J=7.3Hz,1H),6.42(d,J=7.3Hz,1H),3.98(s,2H),3.88(d,J=12.2Hz,2H),3.52(s,2H),3.43-3.34(m,4H),3.22(t,J=6.9Hz,2H),2.73(t,J=6.3Hz,2H),2.57(t,J=7.6Hz,2H),2.24-2.12(m,2H),1.98-1.79(m,6H)。

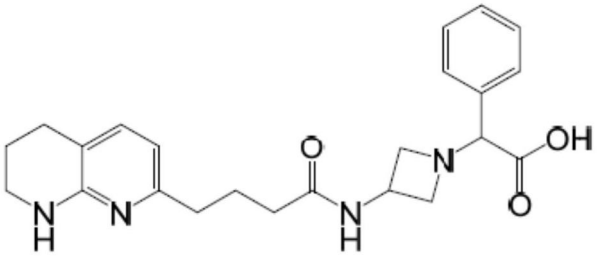
[0873] 2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)丙酸(对映异构化合物44-E1和44-E2)

[0874] 

[0875] 化合物44-E1 LC/MS A:95%纯度,UV=214nm,Rt=1.377min,ESI 374(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.16(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),3.97-3.86(m,1H),3.56-3.37(m,5H),3.14-3.04(m,2H),2.71(t,J=6.2Hz,2H),2.56(t,J=7.6Hz,2H),2.23(t,J=7.5Hz,2H),2.23-2.08(m,2H),1.98-1.78(m,6H),1.51(d,J=7.0Hz,3H)。手性SFC A(45%MeOH):ee 100%,Rt=4.06min。

[0876] 化合物44-E2 LC/MS A:95%纯度,UV=214nm,Rt=1.386min,ESI 374(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.16(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),3.97-3.86(m,1H),3.56-3.37(m,5H),3.14-3.04(m,2H),2.71(t,J=6.2Hz,2H),2.56(t,J=7.6Hz,2H),2.23(t,J=7.5Hz,2H),2.23-2.08(m,2H),1.98-1.78(m,6H),1.51(d,J=7.0Hz,3H)。手性SFC A(45%MeOH):ee 100%,Rt=8.73min。

[0877] 2-苯基-2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-基)乙酸(对映异构化合物45-E1和45-E2)

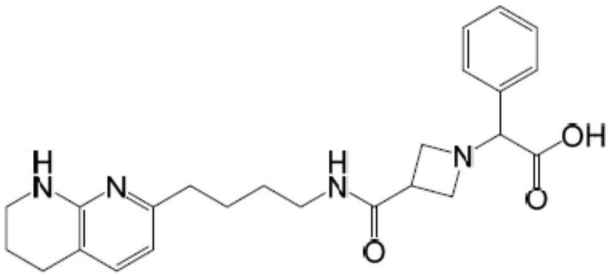
[0878] 

[0879] 化合物45-E1 LC/MS A:99%纯度,UV=214nm,Rt=1.44min,ESI 409.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.41-7.24(m,5H),7.07(d,J=7.3Hz,1H),6.28(d,J=7.2Hz,1H),4.48(s,1H),4.46-4.40(m,1H),4.23(t,J=8.8Hz,1H),3.72-3.70(m,3H),3.28-3.26(m,2H),2.59(t,J=6.2Hz,2H),2.45(t,J=7.2Hz,2H),2.14-2.10(m,2H),1.90-1.65(m,4H)。手性

SFC A(45%MeOH):ee100%,Rt=1.65min

[0880] 化合物45-E2 LC/MS A:99%纯度,UV=214nm,Rt=1.44min,ESI 409.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.41-7.24(m,5H),7.07(d,J=7.3Hz,1H),6.28(d,J=7.2Hz,1H),4.48(s,1H),4.46-4.40(m,1H),4.23(t,J=8.8Hz,1H),3.72-3.70(m,3H),3.28-3.26(m,2H),2.59(t,J=6.2Hz,2H),2.45(t,J=7.2Hz,2H),2.14-2.10(m,2H),1.90-1.65(m,4H)。手性SFC A(45%MeOH):ee100%,Rt=2.72min

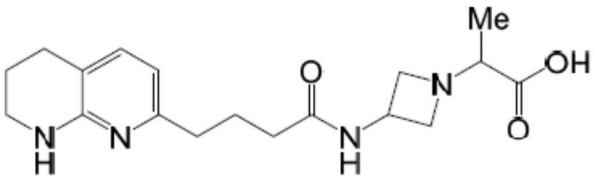
[0881] 2-苯基-2-(3-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)氮杂环丁烷-1-基)乙酸(对映异构化合物46-E1和46-E2)

[0882] 

[0883] 化合物46-E1 LC/MS A:96%纯度,UV=214nm,Rt=1.49min,ESI423.4(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.51-7.48(m,2H),7.44-7.41(m,3H),7.18(d,J=7.6Hz,1H),6.38(d,J=7.2Hz,1H),4.70(s,1H),4.20-4.18(m,1H),4.08-4.03(m,1H),3.99-3.94(m,1H),3.81-3.76(m,1H),3.50-3.46(m,1H),3.39-3.36(m,2H),3.25-3.21(m,1H),2.72-2.69(m,2H),2.57-2.53(m,2H),1.90-1.84(m,2H),1.68-1.62(m,2H),1.57-1.52(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=1.62min。

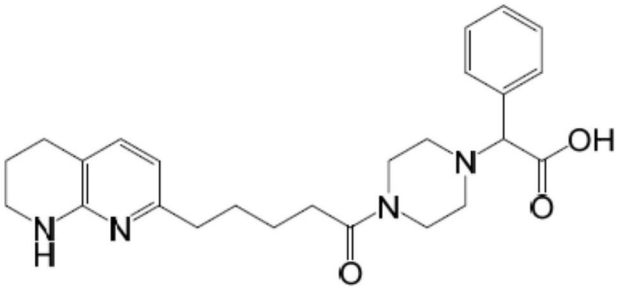
[0884] 化合物46-E2 LC/MS A:96%纯度,UV=214nm,Rt=1.49min,ESI423.3(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.51-7.48(m,2H),7.44-7.41(m,3H),7.18(d,J=7.6Hz,1H),6.38(d,J=7.2Hz,1H),4.70(s,1H),4.20-4.18(m,1H),4.08-4.03(m,1H),3.99-3.94(m,1H),3.81-3.76(m,1H),3.50-3.46(m,1H),3.39-3.36(m,2H),3.25-3.21(m,1H),2.72-2.69(m,2H),2.57-2.53(m,2H),1.90-1.84(m,2H),1.68-1.62(m,2H),1.57-1.52(m,2H)。手性SFC A(45%MeOH):ee 99%,Rt=3.17min。

[0885] 2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)氮杂环丁烷-1-基)丙酸(化合物47)

[0886] 

[0887] 化合物47 LC/MS A:99%纯度,UV=214nm,Rt=1.37min,ESI 347.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.06(d,J=7.1Hz,1H),6.28(d,J=7.2Hz,1H),4.50-4.33(m,1H),4.22(s,1H),4.04(s,1H),3.89-3.39(m,3H),3.36-3.25(m,2H),2.67-2.38(m,4H),2.13(t,J=7.3Hz,2H),1.91-1.70(m,4H),1.24(d,J=6.8Hz,3H)。

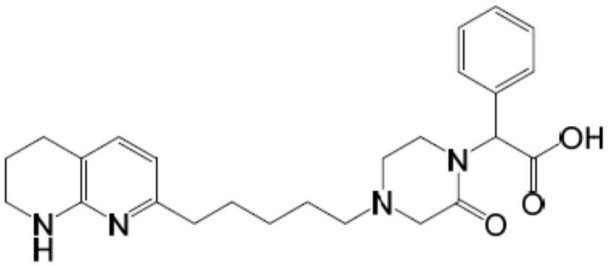
[0888] 2-苯基-2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊酮基)哌嗪-1-基)乙酸(对映异构化合物48-E1和48-E2)

[0889] 

[0890] 化合物48-E1 LC/MS A:99%纯度,UV=214nm,Rt=1.46min,ESI 437.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.54(d,J=7.0Hz,2H),7.39-7.29(m,4H),6.48(d,J=7.3Hz,1H),3.88(s,1H),3.76-3.46(m,4H),3.43-3.37(m,2H),2.77-2.36(m,10H),1.96-1.79(m,2H),1.70-1.59(m,4H)。手性SFC A(40%MeOH):ee 100%,Rt=3.55min。

[0891] 化合物48-E2 LC/MS A:99%纯度,UV=214nm,Rt=1.46min,ESI 437.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.54(d,J=7.0Hz,2H),7.39-7.29(m,4H),6.48(d,J=7.3Hz,1H),3.88(s,1H),3.76-3.46(m,4H),3.43-3.37(m,2H),2.77-2.36(m,10H),1.96-1.79(m,2H),1.70-1.59(m,4H)。手性SFC A(40%MeOH):ee 95%,Rt=4.31min。

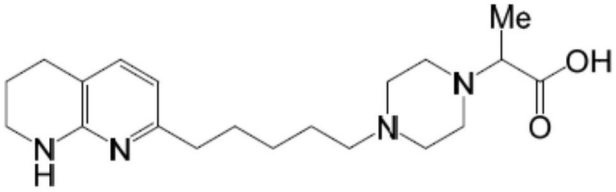
[0892] 2-(2-氧代基-4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)-2-苯基乙酸(对映异构化合物49-E1和49-E2)

[0893] 

[0894] 化合物49-E1 LC/MS A:99%纯度,UV=214nm,Rt=1.53min,ESI437.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.46(d,J=7.3Hz,1H),7.42-7.28(m,5H),6.51(d,J=7.3Hz,1H),6.30(s,1H),3.85-3.68(m,1H),3.59-3.37(m,3H),3.08-2.94(m,2H),2.91-2.50(m,8H),2.02-1.83(m,2H),1.81-1.50(m,6H)。手性SFC A(35%MeOH):ee 100%,Rt=3.5min。

[0895] 化合物49-E2 LC/MS A:96.8%纯度,UV=214nm,Rt=1.53min,ESI437.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.46(d,J=7.3Hz,1H),7.42-7.28(m,5H),6.51(d,J=7.3Hz,1H),6.30(s,1H),3.85-3.68(m,1H),3.59-3.37(m,3H),3.08-2.94(m,2H),2.91-2.50(m,8H),2.02-1.83(m,2H),1.81-1.50(m,6H)。手性SFC A(35%MeOH):ee 97%,Rt=4.48min。

[0896] 2-(4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)丙酸(对映异构化合物50-E1和50-E2)

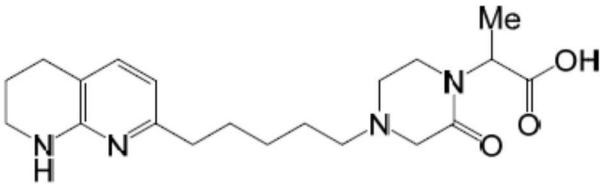
[0897] 

[0898] 化合物50-E1 LC/MS A:100%纯度,UV=214nm,Rt=1.203min,ESI361.0(M+H)+。^{1}H NMR(500MHz,CD_3OD)δ7.13(d,J=9.0Hz,1H),6.35(d,J=9.5Hz,1H),3.39-3.36(m,2H),

3.27-3.25(m,1H),3.03-2.68(m,9H),2.56-2.51(m,4H),1.89-1.86(m,2H),1.69-1.56(m,4H),1.39-1.34(m,6H)。手性SFC B(40%MeOH):ee 100%,Rt=1.51min。

[0899] 化合物50-E2 LC/MS A:100%纯度,UV=214nm,Rt=1.203min,ESI361.0(M+H)+。^{1}H NMR(500MHz,CD_3OD)δ7.11(d,J=9.0Hz,3H),6.36(d,J=9.5Hz,2H),3.39-3.36(m,2H),2.88(q,J=6.8Hz,1H),2.71-2.49(m,11H),2.34(t,J=8.0Hz,2H),1.89-1.86(m,2H),1.69-1.56(m,4H),1.39-1.34(m,6H)。手性SFC B(40%MeOH):ee 100%,Rt=3.47min。

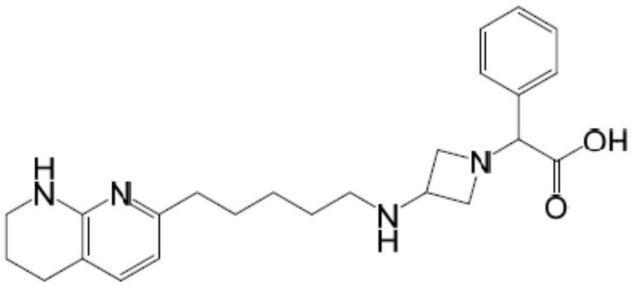
[0900] 2-(2-氧代基-4-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)哌嗪-1-基)丙酸(对映异构化合物51-E1和51-E2)

[0901] 

[0902] 化合物51-E1 LC/MS A:97%纯度,UV=214nm,Rt=1.45min,ESI375.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.42(d,J=7.3Hz,1H),6.48(d,J=7.3Hz,1H),5.01-4.9(m,1H),3.71-3.56(m,1H),3.53-3.34(m,4H),3.23(d,J=17.1Hz,1H),3.10-3.05(m,9.4Hz,2H),2.90-2.71(m,4H),2.67-2.53(m,2H),1.99-1.86(m,2H),1.78-1.49(m,6H),1.45-1.41(m,3H)。手性SFC E(45%MeOH):ee 100%,Rt=3.36min。

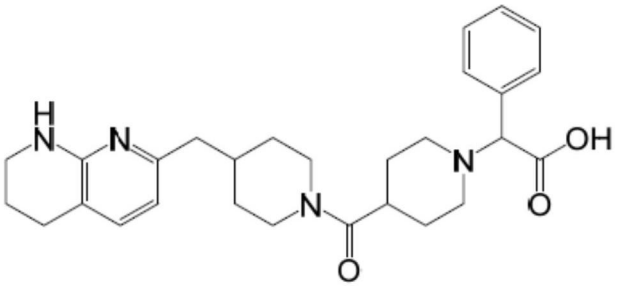
[0903] 化合物51-E2 LC/MS A:96%纯度,UV=214nm,Rt=1.44min,ESI375.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.42(d,J=7.3Hz,1H),6.48(d,J=7.3Hz,1H),5.01-4.9(m,1H),3.71-3.56(m,1H),3.53-3.34(m,4H),3.23(d,J=17.1Hz,1H),3.10-3.05(m,9.4Hz,2H),2.90-2.71(m,4H),2.67-2.53(m,2H),1.99-1.86(m,2H),1.78-1.49(m,6H),1.45-1.41(m,3H)。手性SFC E(45%MeOH):ee 97%,Rt=5.29min。

[0904] 2-苯基-2-(3-((5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)氨基)氮杂环丁烷-1-基)乙酸(化合物52)

[0905] 

[0906] 化合物52 LC/MS A:98.2%纯度,UV=214nm,Rt=1.55min,ESI 409.2(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.49-7.47(m,2H),7.44-7.36(m,3H),7.14(d,J=7.3Hz,1H),6.37(d,J=7.3Hz,1H),4.49(s,1H),4.21-4.16(m,1H),3.77-3.58(m,4H),3.42-3.36(m,2H),2.70(t,J=6.3Hz,2H),2.60(t,J=7.2Hz,2H),2.2(t,J=7.6Hz,2H),1.90-1.85(m,2H),1.69-1.62(m,2H),1.61-1.51(m,2H),1.49-1.34(m,2H)。

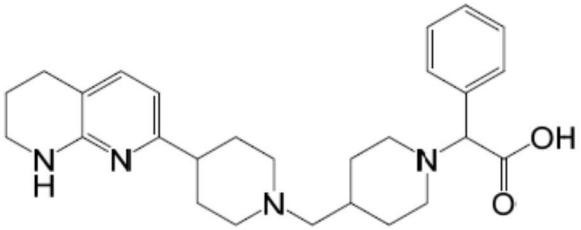
[0907] 2-苯基-2-(4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)哌啶-1-基)乙酸(对映异构化合物53-E1和53-E2)

[0908] 

[0909] 化合物53-E1 LC/MS A:94%纯度,UV=214nm,Rt=1.56min,ESI477.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.58-7.56(m,2H),7.46-7.44(m,3H),7.14(d,J=7.2Hz,1H),6.36-6.33(m,1H),4.57-4.40(m,2H),4.07-3.69(m,2H),3.46-3.35(m,2H),3.16-2.79(m,5H),2.71(t,J=6.1Hz,2H),2.58(m,1H),2.45(t,J=6.6Hz,2H),2.17-1.59(m,9H),1.26-1.00(m,2H)。手性SFC D(25%MeOH):ee 96%,Rt=2.75min。

[0910] 化合物53-E2 LC/MS A:99%纯度,UV=214nm,Rt=1.56min,ESI477.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.58-7.56(m,2H),7.46-7.44(m,3H),7.14(d,J=7.2Hz,1H),6.36-6.33(m,1H),4.57-4.40(m,2H),4.07-3.69(m,2H),3.46-3.35(m,2H),3.16-2.79(m,5H),2.71(t,J=6.1Hz,2H),2.58(m,1H),2.45(t,J=6.6Hz,2H),2.17-1.59(m,9H),1.26-1.00(m,2H)。手性SFC D(25%MeOH):ee 100%,Rt=3.73min。

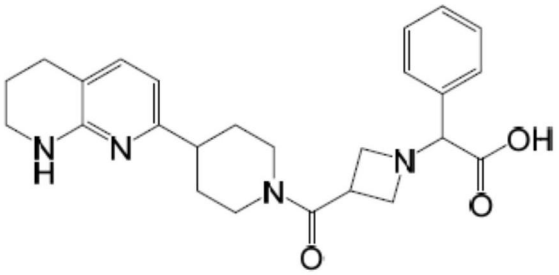
[0911] 2-苯基-2-(4-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-基)甲基)哌啶-1-基)乙酸(对映异构化合物54-E1和54-E2)

[0912] 

[0913] 化合物54-E1 LC/MS A:100%纯度,UV=214nm,Rt=1.59min,ESI449.4(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.59-7.55(m,2H),7.45-7.42(m,3H),7.15(d,J=7.6Hz,1H),6.36(d,J=7.2Hz,1H),4.35(s,1H),3.69-3.65(brs,1H),3.38-3.35(m,2H),3.09-3.06(m,2H),2.98-2.95(m,1H),2.89-2.83(m,1H),2.71-2.67(m,3H),2.48-2.40(m,1H),2.37-2.35(m,2H),2.20-2.10(m,2H),2.00-1.97(m,1H),1.89-1.71(m,8H),1.60-1.41(m,1H)。手性SFC A(40%MeOH):ee 100%,Rt=2.51min。

[0914] 化合物54-E2 LC/MS A:100%纯度,UV=214nm,Rt=1.59min,ESI449.4(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.59-7.55(m,2H),7.44-7.41(m,3H),7.14(d,J=7.6Hz,1H),6.37(d,J=7.6Hz,1H),4.35(s,1H),3.70-3.69(brs,1H),3.38-3.35(m,2H),3.09-3.06(m,2H),2.98-2.95(m,1H),2.89-2.83(m,1H),2.71-2.68(m,3H),2.47-2.40(m,1H),2.37-2.35(m,2H),2.19-2.19(m,2H),2.02-1.97(m,1H),1.90-1.71(m,8H),1.59-1.41(m,1H)。手性SFC A(40%MeOH):ee 97%,Rt=3.75min。

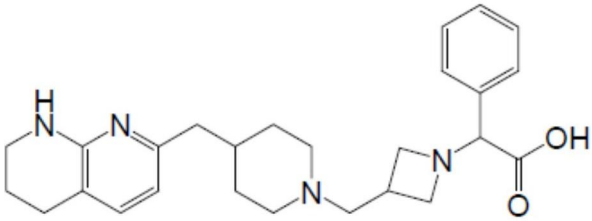
[0915] 2-苯基-2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(对映异构化合物55-E1和55-E2)

[0916] 

[0917] 化合物55-E1 LC/MS A:97.7%纯度,UV=214nm,Rt=1.0min,ESI 435.2(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.42-7.40(m,2H),7.35-7.32(m,3H),7.04(d,J=6.0Hz,1H),6.26(dd,J=7.2Hz,2.4Hz,1H),4.59(s,1H),4.52-4.50(m,1H),4.24-4.22(m,1H),4.11-4.07(m,1H),4.00-3.93(m,1H),3.83-3.76(m,2H),3.59-3.56(m,1H),3.28-3.26(m,2H),3.06-3.01(m,1H),2.68-2.56(m,4H),1.77-1.75(m,4H),1.54-1.45(m,2H)。手性SFC A(40%MeOH):ee 100%,Rt=2.39min。

[0918] 化合物55-E2 LC/MS A:96.7%纯度,UV=214nm,Rt=1.0min,ESI 435.2(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ7.41-7.40(m,2H),7.34-7.32(m,3H),7.04(d,J=6.0Hz,1H),6.26(dd,J=7.2Hz,1.6Hz,1H),4.57(s,1H),4.53-4.50(m,1H),4.23-4.21(m,1H),4.10-4.06(m,1H),3.97-3.90(m,1H),3.83-3.75(m,2H),3.59-3.54(m,1H),3.28-3.26(m,2H),3.06-3.01(m,1H),2.69-2.56(m,4H),1.77-1.75(m,4H),1.54-1.45(m,2H)。手性SFC A(40%MeOH):ee 100%,Rt=4.37min。

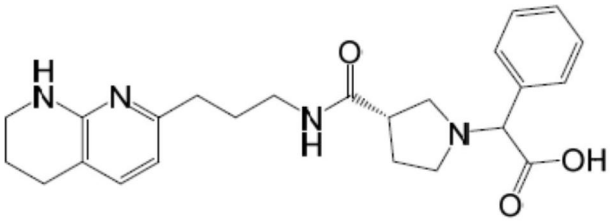
[0919] 2-苯基-2-(3-((4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-基)甲基)氮杂环丁烷-1-基)乙酸(对映异构化合物56-E1和56-E2)

[0920] 

[0921] 化合物56-E1 LC/MS A:99%纯度,UV=214nm,Rt=1.53min,ESI 435.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.55-7.33(m,5H),7.12(d,J=7.3Hz,1H),6.32(d,J=7.3Hz,1H),4.59(s,1H),4.17-4.13(m,1H),3.70(d,J=8.1Hz,2H),3.53.57-3.39(m,1H),3.44-3.34(m,2H),3.02-2.98(m,1H),2.84(d,J=11.3Hz,2H),2.74-2.61(m,4H),2.42(d,J=6.8Hz,2H),2.03(t,J=11.7Hz,2H),1.93-1.80(m,2H),1.67-1.61(m,3H),1.32-1.26(m,2H)。手性SFC A(45%MeOH):ee 51%,Rt=2.89min。

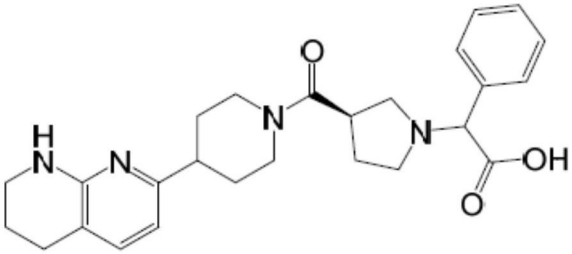
[0922] 化合物56-E2 LC/MS A:99%纯度,UV=214nm,Rt=1.53min,ESI 435.4(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.55-7.33(m,5H),7.12(d,J=7.3Hz,1H),6.32(d,J=7.3Hz,1H),4.59(s,1H),4.17-4.13(m,1H),3.70(d,J=8.1Hz,2H),3.53.57-3.39(m,1H),3.44-3.34(m,2H),3.02-2.98(m,1H),2.84(d,J=11.3Hz,2H),2.74-2.61(m,4H),2.42(d,J=6.8Hz,2H),2.03(t,J=11.7Hz,2H),1.93-1.80(m,2H),1.67-1.61(m,3H),1.32-1.26(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=3.84min。

[0923] 2-苯基-2-((S)-3-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)吡咯烷-1-基)乙酸(化合物57)

[0924] 

[0925] 化合物57/MS B:100%纯度,UV=214nm,Rt=1.22min,ESI 423.3(M+H)+。^{1}H NMR(400MHz,CD_3OD)δ8.49(s,1.6H,甲酸盐),7.58-7.43(m,6H),6.52(d,J=7.2Hz,1H),4.70(s,0.6H),4.56(s,0.4H),3.65-3.56(m,1H),3.47-3.39(m,3H),3.29-3.01(m,5H),2.77(t,J=6Hz,2H),2.67(t,J=6Hz,2H),2.36-2.10(m,2H),1.95-1.82(m,4H)。

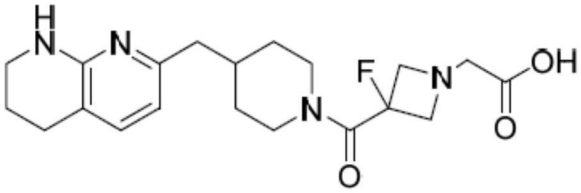
[0926] 2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)吡咯烷-1-基)乙酸(对映异构化合物58-E1和58-E2)

[0927] 

[0928] 化合物58-E1 LC/MS B:97%纯度,UV=214nm,Rt=1.24min,ESI 449.3(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.62-7.59(m,2H),7.45-7.44(m,3H),7.15(d,J=7.4Hz,1H),6.37(t,J=7.0Hz,1H),4.65-4.61(m,2H),4.06(d,J=13.3Hz,1H),3.73-3.57(m,2H),3.38(t,J=5.6Hz,3H),3.25-3.14(m,3H),2.75-2.68(m,4H),2.41-2.35(m,1H),2.22-2.10(m,1H),1.96-1.84(m,4H),1.64-1.58(m,2H)。手性SFC B(35%MeOH):ee 98%,Rt=2.15min。

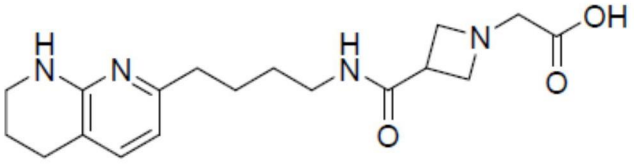
[0929] 化合物58-E2 LC/MS B:93%纯度,UV=214nm,Rt=1.24min,ESI 449.3(M+H)+。^{1}H NMR(400MHz,MeOD)δ7.60-7.58(m,2H),7.45-7.43(m,3H),7.14(d,J=7.2Hz,1H),6.37(dd,J_1=7.4Hz,3.1Hz,1H),4.65-4.58(m,2H),4.08(d,J=13.0Hz,1H),3.72-3.60(m,2H),3.38(t,J=5.6Hz,3H),3.25-3.18(m,2H),3.04-2.98(m,1H),2.76-2.68(m,4H),2.36-2.27(m,1H),2.17-2.06(m,1H),1.95-1.86(m,4H),1.70-1.54(m,2H)。手性SFC B(35%MeOH):ee 99%,Rt=3.15min。

[0930] 2-(3-氟-3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(化合物59)

[0931] 

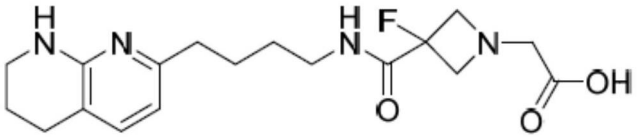
[0932] 化合物59 LC/MS B:100%纯度,UV=214nm,Rt=1.05min,ESI 391(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.22(d,J=7.3Hz,1H),6.38(d,J=7.3Hz,1H),4.49-4.35(m,1H),4.32-4.10(m,2H),4.03-3.86(m,2H),3.67(m,1H),3.51-3.34(m,4H),3.05(t,J=15.4Hz,1H),2.74-2.68(m,3H),2.57-2.41(m,2H),1.98-1.85(m,3H),1.91-1.81(m,2H),1.33-1.06(m,2H)。

[0933] 2-(3-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)氮杂环丁烷-1-基)乙酸(化合物60)

[0934] 

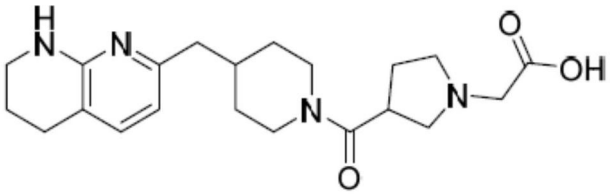
[0935] 化合物60LC/MS B:100%纯度,UV=214nm,Rt=1.06min。ESI 347.1$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ8.47(s,1H),7.45(d,J=7.3Hz,1H),6.53(d,J=7.3Hz,1H),4.36-4.27(m,4H),3.82(s,2H),3.64-3.54(m,1H),3.50-3.43(m,2H),3.30(t,J=6.8Hz,2H),2.82-2.76(m,2H),2.73-2.65(m,2H),1.98-1.89(m,2H),1.78-1.66(m,2H),1.65-1.54(m,2H)。

[0936] 2-(3-氟-3-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)氮杂环丁烷-1-基)乙酸(化合物61)

[0937] 

[0938] 化合物61 LC/MS A:100%纯度,UV=214nm,Rt=1.49min,ESI 365.2$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.20(d,J=7.3Hz,1H),6.41(d,J=7.2Hz,1H),3.92(dd,J=20.0,10.4Hz,2H),3.76(dd,J=20.6,10.3Hz,2H),3.44-3.38(m,2H),3.36-3.28(m,4H),2.73(t,J=6.3Hz,2H),2.57(t,J=7.6Hz,2H),1.92-1.85(m,2H),1.71-1.55(m,4H)。

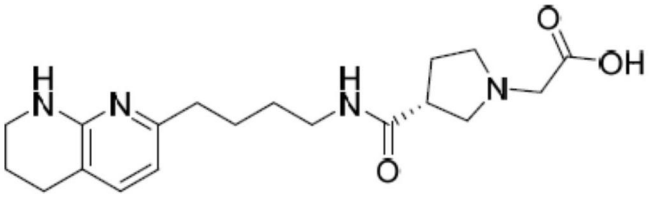
[0939] 2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)吡咯烷-1-基)乙酸(对映异构化合物62-E1和62-E2)

[0940] 

[0941] 化合物62-E1 LC/MS A:100%纯度,UV=214nm,R_t=1.54min,ESI 387.3$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.16(d,J=7.3Hz,1H),6.37(d,J=7.2Hz,1H),4.53-4.45(m,1H),4.02-3.94(m,1H),3.85-3.65(m,4H),3.58-3.36(m,5H),3.14-3.06(m,1H),2.74-2.61(m,3H),2.45(dd,J=34.6,7.4Hz,3H),2.18-2.04(m,1H),2.01-1.85(m,3H),1.79-1.66(m,2H),1.26-1.11(m,2H)。手性SFC B(40%MeOH):ee 95%,Rt=1.24min。

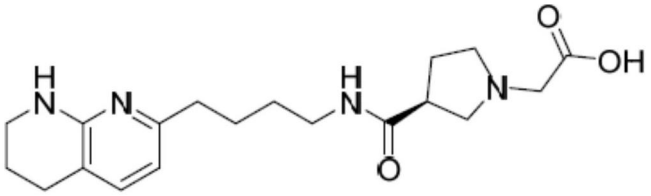
[0942] 化合物62-E2 LC/MS A:100%纯度,UV=214nm,R_t=1.54min,ESI 387.3$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.16(d,J=7.3Hz,1H),6.37(d,J=7.1Hz,1H),4.54-4.45(m,1H),4.02-3.95(m,1H),3.86-3.63(m,4H),3.60-3.36(m,5H),3.10(td,J=13.3,2.7Hz,1H),2.76-2.59(m,3H),2.51-2.34(m,3H),2.20-2.06(m,1H),2.02-1.83(m,3H),1.80-1.66(m,2H),1.28-1.08(m,2H)。手性SFC B(40%MeOH):ee 96%,Rt=2.45min

[0943] (R)-2-(3-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)吡咯烷-1-基)乙酸(化合物63)

[0944] 

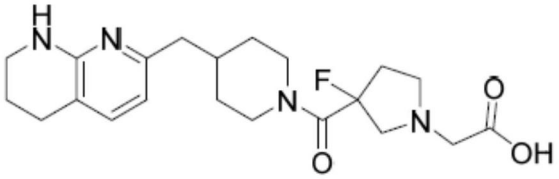
[0945] 化合物63 LC/MS A:100%纯度,UV=214nm,Rt=1.43min,ESI 361.4(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.24(d,J=7.3Hz,1H),6.41(d,J=7.3Hz,1H),3.62(d,J=15.8Hz,1H),3.43-3.13(m,7H),3.07-2.97(m,3H),2.74(t,J=6.3Hz,2H),2.66-2.60(m,1H),2.56-2.47(m,1H),2.31-2.23(m,1H),2.09-2.01(m,1H),1.94-1.87(m,2H),1.81-1.71(m,1H),1.69-1.50(m,3H)。

[0946] (S)-2-(3-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)吡咯烷-1-基)乙酸(化合物64)

[0947] 

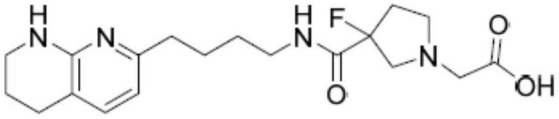
[0948] 化合物64 LC/MS A:100%纯度,UV=214nm,Rt=1.43min,ESI 361.4(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.26(d,J=7.2Hz,1H),6.42(d,J=7.3Hz,1H),3.69(d,J=15.9Hz,1H),3.52-3.38(m,4H),3.38-3.28(m,2H),3.22-3.13(m,1H),3.10-3.01(m,3H),2.77-2.71(m,2H),2.68-2.61(m,1H),2.57-2.48(m,1H),2.36-2.25(m,1H),2.12-2.03(m,1H),1.96-1.86(m,2H),1.83-1.71(m,1H),1.69-1.51(m,3H)。

[0949] 2-(3-氟-3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)吡咯烷-1-基)乙酸(化合物65)

[0950] 

[0951] 化合物65 LC/MS A:100%纯度,UV=214nm,Rt=1.45min,ESI 405.2(M+H)$^+$。^{1}H NMR(500MHz,DMSO-d_6)δ7.23(d,J=7.3Hz,1H),7.12(s,1H),6.36(d,J=7.3Hz,1H),4.29(d,J=12.8Hz,1H),3.98(d,J=13.4Hz,1H),3.39-3.11(m,6H),3.05-2.91(m,2H),2.70-2.52(m,5H),2.44(d,J=7.2Hz,2H),2.21-2.04(m,1H),1.99-1.87(m,1H),1.81-1.72(m,2H),1.67-1.55(m,2H),1.18-0.96(m,2H)。

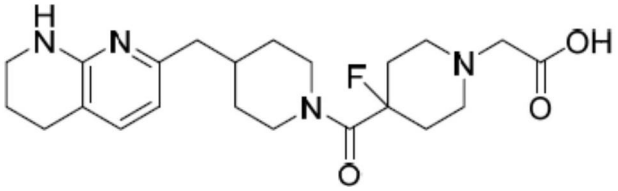
[0952] 2-(3-氟-3-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)吡咯烷-1-基)乙酸(化合物66)

[0953] 

[0954] 化合物66 LC/MS A:100%纯度,UV=214nm,Rt=1.59min,ESI 379.3(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.37(d,J=7.3Hz,1H),6.47(d,J=7.3Hz,1H),3.59-3.50(m,2H),

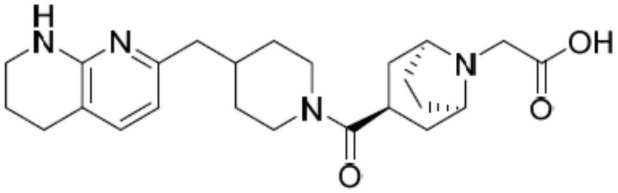
3.48-3.40(m,3H),3.38-3.30(m,1H),3.26-3.05(m,4H),2.79-2.68(m,3H),2.61-2.42(m,2H),2.32-2.19(m,1H),1.95-1.89(m,2H),1.85-1.54(m,4H)。

[0955] 2-(4-氟-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)哌啶-1-基)乙酸(化合物67)

[0956] 

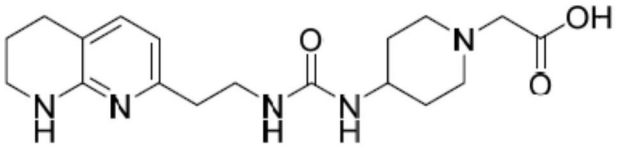
[0957] 化合物67 LC/MS A:100%纯度,UV=214nm,Rt=1.59min,ESI 419.3$(M+H)^+$。^1H NMR(500MHz,DMSO-d_6)δ7.13(d,J=7.3Hz,1H),6.33(d,J=7.3Hz,1H),4.32-4.13(m,2H),3.42-3.25(m,6H),3.08-2.97(m,3H),2.68-2.60(m,3H),2.43-2.27(m,4H),2.21-2.08(m,2H),1.94-1.84(m,1H),1.81-1.72(m,2H),1.68-1.59(m,2H),1.19-0.99(m,2H)。

[0958] 2-((1R,3s,5S)-3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)-8-氮杂二环[3.2.1]辛烷-8-基)乙酸(化合物68)

[0959] 

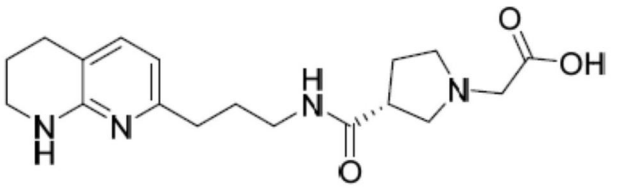
[0960] 化合物68 LC/MS B:100%纯度,UV=214nm,Rt=1.05min,ESI 427.0$(M+H)^+$。^1H NMR(400MHz,甲醇-d_4)δ5.87(d,J=7.3Hz,1H),4.93(d,J=7.3Hz,1H),2.90(d,J=13.3Hz,1H),2.55-2.39(m,3H),1.98(s,2H),1.73-1.62(m,2H),1.51(t,J=12.6Hz,1H),1.23-1.13(m,2H),1.07-0.93(m,3H),0.75-0.04(m,14H),-0.29--0.54(m,2H)。

[0961] 2-(4-(3-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)脲基)哌啶-1-基)乙酸(化合物69)

[0962] 

[0963] 化合物69 LC/MS A:97%纯度,UV=254nm,Rt=1.34min,ESI 362.2$(M+H)^+$。^1H NMR(500MHz,甲醇-d_4)δ7.16(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),3.78-3.68(m,1H),3.55(s,2H),3.53-3.45(m,2H),3.44-3.37(m,4H),3.13-3.00(m,2H),2.74-2.65(m,4H),2.12-2.03(m,2H),1.93-1.85(m,2H),1.80-1.69(m,2H)。

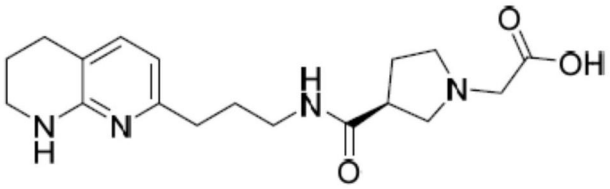
[0964] (R)-2-(3-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)吡咯烷-1-基)乙酸(化合物70)

[0965] 

[0966] 化合物70LC/MS A:100%纯度,UV=214nm,Rt=1.46min,ESI 347$(M+H)^+$。^1H NMR

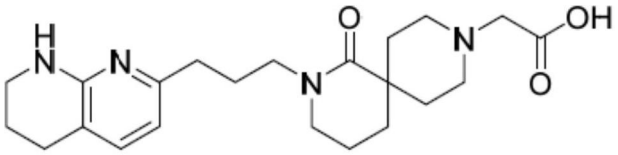
(400MHz,MeOD)δ7.19(d,J=7.3Hz,1H),6.41(d,J=7.3Hz,1H),3.66(dd,J=35.1,15.9Hz,2H),3.56-3.31(m,5),3.32-3.08(m,4H),2.71(t,J=6.2Hz,2H),2.63-2.49(m,2H),2.33(m,1H),2.13(m,1H),1.94-1.77(m,4H)。手性SFC B(40%MeOH):ee 100%,Rt=2.12min。

[0967] (S)-2-(3-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)吡咯烷-1-基)乙酸(化合物71)

[0968] 

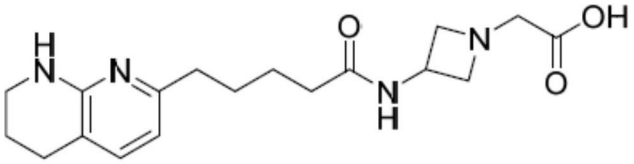
[0969] 化合物71 LC/MS A:100%纯度,UV=214nm,Rt=1.45min,ESI 347.2$(M+H)^+$。^1H NMR(500MHz,甲醇-d_4)δ7.19(d,J=7.3Hz,1H),6.41(d,J=7.3Hz,1H),3.68(d,J=15.9Hz,1H),3.59(d,J=15.9Hz,1H),3.51-3.43(m,1H),3.43-3.34(m,4H),3.29-3.11(m,4H),2.76-2.69(m,2H),2.63-2.51(m,2H),2.37-2.26(m,1H),2.18-2.08(m,1H),1.95-1.80(m,4H)。手性SFC B(40%MeOH):ee 100%,Rt=1.77min。

[0970] 2-(1-氧代基-2-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-2,9-二氮杂螺[5.5]十一烷-9-基)乙酸(化合物72)

[0971] 

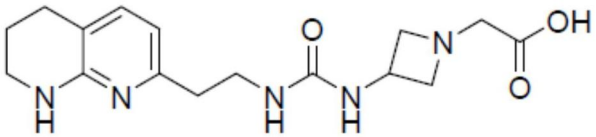
[0972] 化合物72 LC/MS A:100%纯度,UV=214nm,Rt=1.69min,ESI 401.3$(M+H)^+$。^1H NMR(500MHz,MeOD)δ7.14(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),3.60(d,J=16.7Hz,4H),3.44-3.35(m,6H),3.19(s,2H),2.71(t,J=6.2Hz,2H),2.53(t,J=7.7Hz,2H),2.29(s,2H),1.96-1.81(m,8H),1.81-1.69(m,2H)。

[0973] 2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊酰氨基)氮杂环丁烷-1-基)乙酸(化合物73)

[0974] 

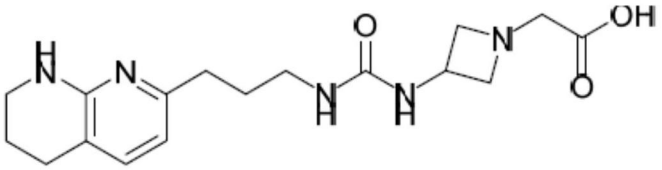
[0975] 化合物73 LC/MS A:100%纯度,UV=214nm,Rt=1.51min,ESI 347.3$(M+H)^+$。^1H NMR(500MHz,甲醇-d_4)δ7.19(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),4.58(p,J=7.4Hz,1H),4.37-4.30(m,2H),4.05-3.97(m,2H),3.74(s,2H),3.43-3.37(m,2H),2.72(t,J=6.3Hz,2H),2.61-2.52(m,2H),2.30-2.22(m,2H),1.94-1.84(m,2H),1.71-1.60(m,4H)。

[0976] 2-(3-(3-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)脲基)氮杂环丁烷-1-基)乙酸(化合物74)

[0977] 

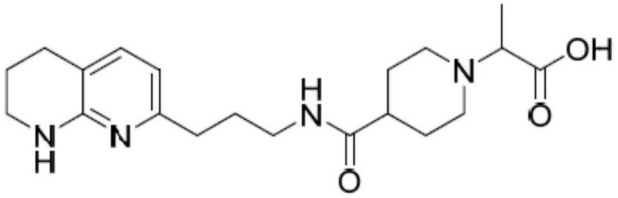
[0978] 化合物74 LC/MS A:100%纯度,UV=214nm,Rt=1.34min,ESI 334(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.21(d,J=7.3Hz,1H),6.43(d,J=7.3Hz,1H),4.52(brs,1H),4.36(t,J=8.6Hz,2H),4.14-4.01(m,2H),3.80(s,2H),3.41(d,J=7.0Hz,4H),2.79-2.65(m,4H),1.96-1.82(m,2H)。

[0979] 2-(3-(3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)脲基)氮杂环丁烷-1-基)乙酸(化合物75)

[0980] 

[0981] 化合物75 LC/MS C:100%纯度,UV=214nm,Rt=1.49min,ESI 348.2(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.15(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.54-4.45(m,1H),4.23(t,J=9.1Hz,2H),3.89-3.80(m,2H),3.64(s,2H),3.42-3.36(m,2H),3.14(t,J=6.9Hz,2H),2.71(t,J=6.2Hz,2H),2.59-2.49(m,2H),1.90-1.78(m,4H)。

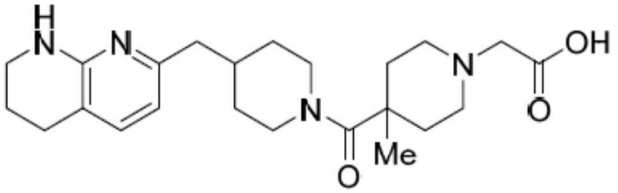
[0982] 2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(对映异构化合物76-E1和76-E2)

[0983] 

[0984] 化合物76-E1 LC/MS A:96%纯度,UV=214nm,Rt=1.41min,ESI 375.2(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.16(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),3.64-3.52(m,3H),3.41-3.37(m,2H),3.22(t,J=6.9Hz,2H),3.15-2.99(m,2H),2.72(t,J=6.4Hz,2H),2.58-2.45(m,3H),2.10-1.96(m,4H),1.93-1.78(m,4H),1.52(d,J=7.1Hz,3H)。手性SFC B(30%MeOH):ee 100%,Rt=1.98min。

[0985] 化合物76-E2 LC/MS A:100%纯度,UV=214nm,Rt=0.91min,ESI 375.3(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.16(d,J=7.2Hz,1H),6.39(d,J=7.4Hz,1H),3.66-3.50(m,3H),3.42-3.37(m,2H),3.22(t,J=7.0Hz,2H),3.15-2.98(m,2H),2.72(t,J=6.3Hz,2H),2.55(t,J=7.7Hz,2H),2.52-2.45(m,1H),2.11-1.97(m,4H),1.93-1.80(m,4H),1.52(d,J=7.2Hz,3H)。手性SFC B(30%MeOH):ee 99%,Rt=3.36min。

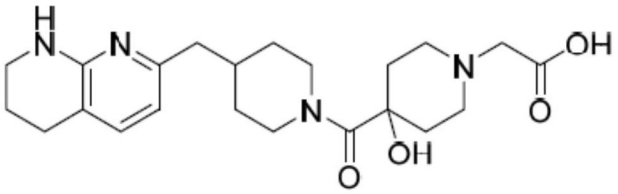
[0986] 2-(4-甲基-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)哌啶-1-基)乙酸(化合物77)

[0987] 

[0988] 化合物77 LC/MS A:100%纯度,UV=214nm,Rt=1.61min,ESI 415.3(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.15(d,J=7.3Hz,1H),6.37(d,J=7.1Hz,1H),4.36(d,J=12.9Hz,

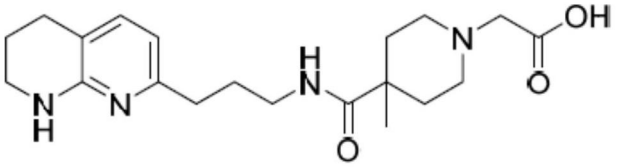
2H),3.58(s,2H),3.53-3.42(m,2H),3.43-3.36(m,2H),3.21-3.08(m,2H),2.98-2.78(m,2H),2.72(t,J=6.3Hz,2H),2.47(d,J=7.2Hz,2H),2.40(d,J=15.0Hz,2H),2.03-1.93(m,1H),1.92-1.79(m,4H),1.75-1.67(m,2H),1.38(s,3H),1.23-1.12(m,2H)。

[0989] 2-(4-羟基-4-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)哌啶-1-基)乙酸(化合物78)

[0990] 

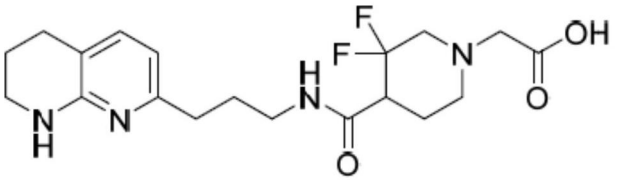
[0991] 化合物78 LC/MS A:100%纯度,UV=214nm,Rt=1.46min,ESI 417$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.15(d,J=7.3Hz,1H),6.35(d,J=7.3Hz,1H),4.83(s,1H),4.50(brs,1H),3.53(brs,1H),3.47-3.34(m,2H),3.22(m,3H),3.01(s,1H),2.71(t,J=6.1Hz,2H),2.60(brs,1H),2.46(d,J=7.1Hz,2H),2.33(brs,1H),1.98(d,J=14.6Hz,2H),1.91-1.82(m,2H),1.69(d,J=11.9Hz,21H),1.21(brs,2H)。

[0992] 2-(4-甲基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物79)

[0993] 

[0994] 化合物79 LC/MS A:100%纯度,UV=214nm,Rt=1.41min,ESI 375.4$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.22(d,J=7.3Hz,1H),6.43(d,J=7.3Hz,1H),3.56(s,2H),3.42-3.37(m,2H),3.32-3.17(m,6H),2.73(t,J=6.3Hz,2H),2.62-2.56(m,2H),2.36-2.26(m,2H),1.94-1.81(m,4H),1.79-1.70(m,2H),1.24(s,3H)。

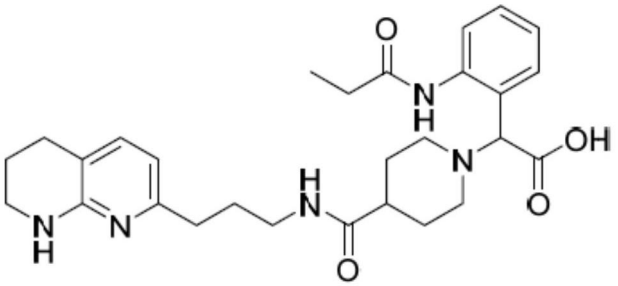
[0995] 2-(3,3-二氟-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物80)

[0996] 

[0997] 化合物80LC/MS A:100%纯度,UV=214nm,Rt=1.48min,ESI 397.2$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.51(d,J=7.3Hz,1H),6.57(d,J=7.3Hz,1H),3.48(t,J=5.6Hz,2H),3.39-3.33(m,2H),3.28-3.17(m,3H),3.08-3.01(m,1H),2.92-2.64(m,6H),2.56(t,J=11.1Hz,1H),2.17-2.05(m,1H),1.97-1.85(m,5H)。

[0998] 2-(2-丙酰氨基苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物81)

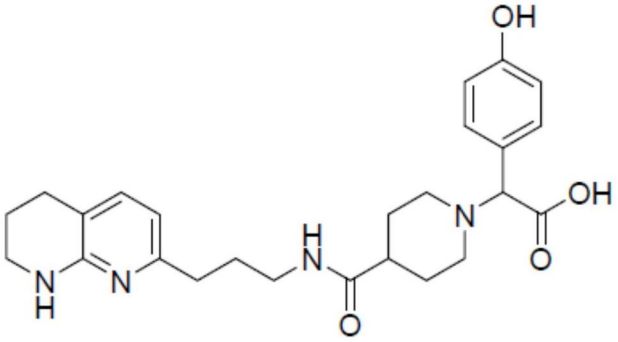
[0999]



[1000] 化合物81 LC/MS A:100%纯度,UV=214nm,Rt=1.46min,ESI 508.4(M+H)+。^{1}H NMR(500MHz,MeOD)δ8.40(s,1H),7.69(s,1H),7.55(s,1H),7.42(s,2H),7.29(s,1H),6.54(d,J=7.2Hz,1H),3.66(s,1H),3.49-3.40(m,2H),3.26(m,4H),2.96-2.25(m,9H),2.15-1.69(m,8H),1.29(t,J=7.6Hz,3H)。

[1001] 2-(4-羟苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物82)

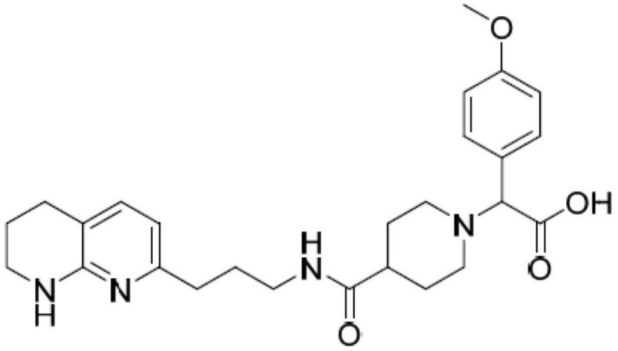
[1002]



[1003] 化合物82 LC/MS A:99%纯度,UV=214nm,Rt=1.45min,ESI 453(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.39(d,J=8.6Hz,2H),7.15(d,J=7.3Hz,1H),6.85(d,J=8.4Hz,2H),6.38(d,J=7.3Hz,1H),4.37(s,1H),3.72(s,1H),3.42-3.37(m,2H),3.20(t,J=6.9Hz,2H),3.10(s,1H),2.95(s,1H),2.71(t,J=6.2Hz,3H),2.57-2.51(m,2H),2.43(s,1H),2.05-1.80(m,8H)。

[1004] 2-(4-甲氧基苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物83)

[1005]

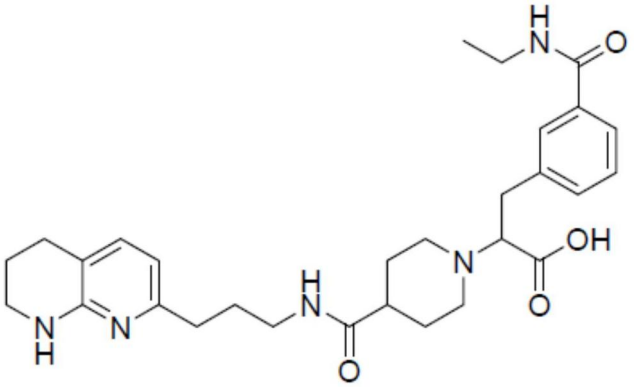


[1006] 化合物83 LC/MS A:98%纯度,UV=214nm,Rt=1.49min,ESI 467.2(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.49(d,J=8.7Hz,2H),7.16(d,J=7.3Hz,1H),6.99(d,J=8.7Hz,2H),6.38(d,J=7.4Hz,1H),4.38(s,1H),3.82(s,3H),3.76-3.68(m,1H),3.40-3.35(m,2H),3.20(t,J=6.9Hz,2H),3.12-3.02(m,1H),2.95-2.84(m,1H),2.81-2.72(m,1H),2.70(t,J

＝6.3Hz,2H),2.54(t,J＝7.6Hz,2H),2.47-2.39(m,1H),2.08-1.77(m,8H)。

[1007] 3-(3-(乙基氨甲酰基)苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(化合物84)

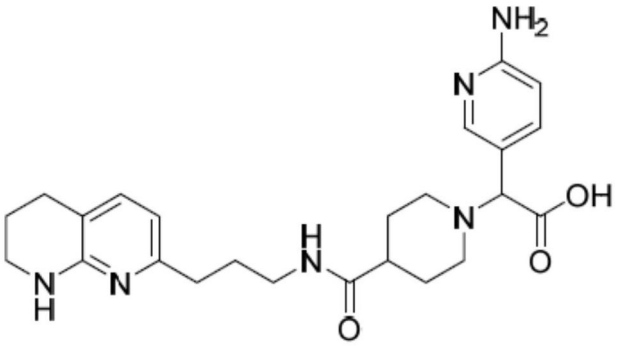
[1008]



[1009] 化合物84 LC/MS A:98%纯度,UV＝214nm,Rt＝1.45min,ESI 522.0$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.74(t,J＝1.9Hz,1H),7.71-7.66(m,1H),7.52-7.48(m,1H),7.43-7.38(m,1H),7.23(d,J＝7.4Hz,1H),6.43(d,J＝7.4Hz,1H),3.67(t,J＝7.1Hz,1H),3.59-3.46(m,2H),3.45-3.37(m,4H),3.26-3.20(m,4H),3.02-2.91(m,2H),2.73(t,J＝6.3Hz,2H),2.58(t,J＝7.7Hz,2H),2.49-2.38(m,1H),2.00-1.78(m,8H),1.25(t,J＝7.3Hz,3H)。

[1010] 2-(6-氨基吡啶-3-基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物85)

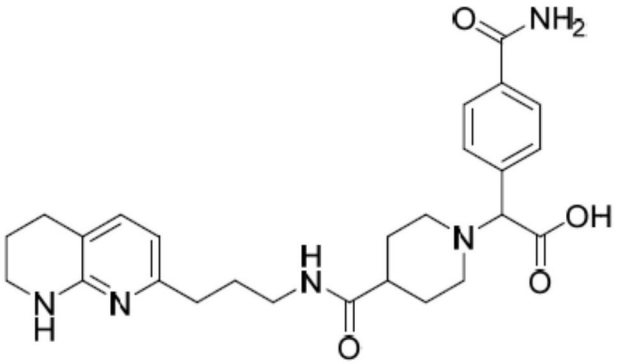
[1011]



[1012] 化合物85 LC/MS A:100%纯度,UV＝214nm,Rt＝0.90min,ESI 453$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ8.01(d,J＝1.4Hz,1H),7.66(dd,J＝8.7,2.2Hz,1H),7.14(d,J＝7.2Hz,1H),6.62(d,J＝8.8Hz,1H),6.38(d,J＝7.3Hz,1H),4.18(s,1H),3.60(brs,1H),3.44-3.35(m,2H),3.20(t,J＝6.9Hz,2H),3.07(m,1H),2.83-2.65(m,3H),2.58-2.49(m,2H),2.41-2.31(m,1H),2.03-1.76(m,8H)。

[1013] 2-(4-氨甲酰基苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物86)

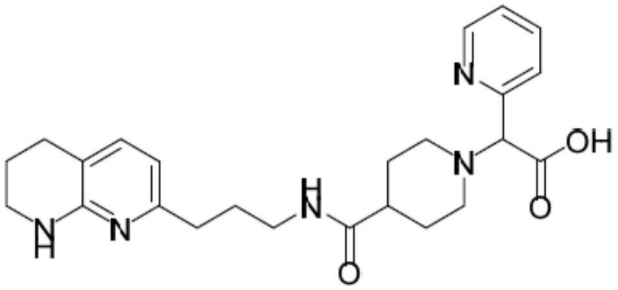
[1014]



[1015] 化合物86 LC/MS A:100%纯度,UV=214nm,Rt=0.90min,ESI 480(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.94(d,J=8.3Hz,2H),7.69(d,J=8.3Hz,2H),7.19(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),4.43(s,1H),3.73(brs,1H),3.44-3.35(m,2H),3.21(t,J=6.9Hz,2H),3.12-2.97(m,1H),2.87(m,1H),2.79-2.67(m,3H),2.62-2.49(m,2H),2.43(m,1H),2.11-1.92(m,3H),1.88(m,3H),1.82(m,2H)。

[1016] 2-(吡啶-2-基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物87)

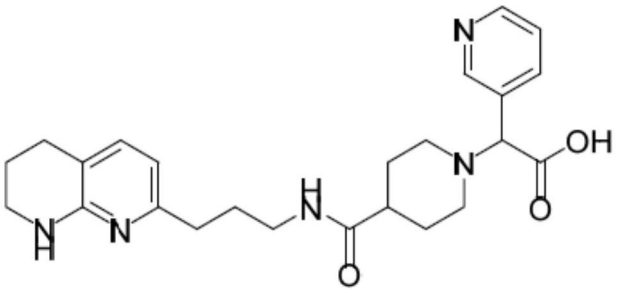
[1017]



[1018] 化合物87 LC/MS A:100%纯度,UV=214nm,Rt=1.54min,ESI 438(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ8.59(d,J=4.3Hz,1H),7.86(td,J=7.7,1.7Hz,1H),7.67(d,J=7.8Hz,1H),7.41-7.37(m,1H),7.25(d,J=7.3Hz,1H),6.42(d,J=7.3Hz,1H),4.48(s,1H),3.66(d,J=10.9Hz,1H),3.45-3.38(m,2H),3.20(t,J=6.8Hz,2H),3.07(d,J=11.4Hz,1H),2.76-2.52(m,6H),2.44-2.36(m,1H),1.97-1.79(m,8H)。

[1019] 2-(吡啶-3-基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物88)

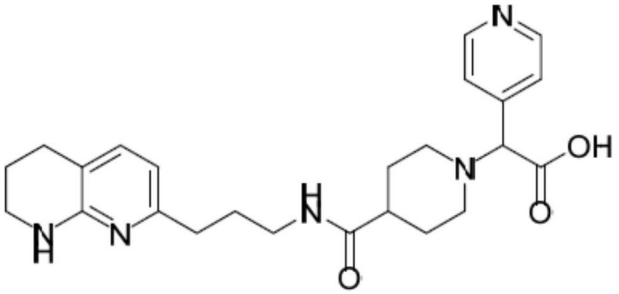
[1020]



[1021] 化合物88 LC/MS A:100%纯度,UV=214nm,Rt=1.48min,ESI 438(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ8.72(s,1H),8.57(d,J=4.2Hz,1H),8.07(d,J=8.0Hz,1H),7.50(dd,J=7.8,4.9Hz,1H),7.27(d,J=7.3Hz,1H),6.45(d,J=7.3Hz,1H),4.34(s,1H),3.63(s,1H),3.44-3.37(m,2H),3.22(t,J=6.8Hz,2H),3.02(d,J=11.6Hz,1H),2.74(t,J=6.2Hz,3H),

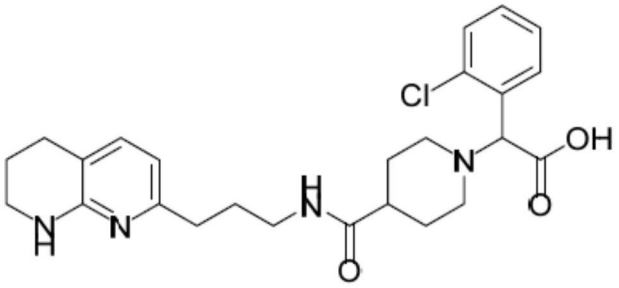
2.64-2.48(m,3H),2.39(dd,J=12.8,8.5Hz,1H),2.04-1.79(m,8H)。

[1022] 2-(吡啶-4-基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物89)

[1023] 

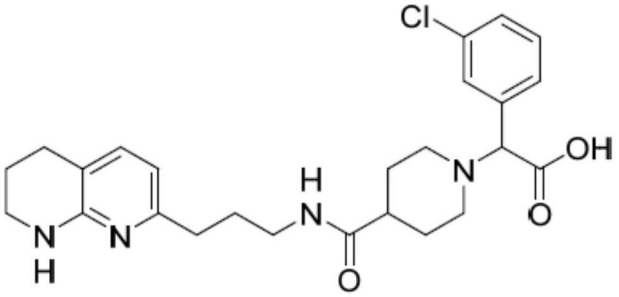
[1024] 化合物89 LC/MS A:100%纯度,UV=214nm,Rt=1.38min,ESI 438$(M+H)^+$。^{1}H NMR(500MHz,DMSO)δ8.51(d,J=5.3Hz,2H),7.76(t,J=5.3Hz,1H),7.33(d,J=5.0Hz,2H),7.05(d,J=7.3Hz,1H),6.35(s,1H),6.27(d,J=7.2Hz,1H),3.52(s,1H),3.24(s,2H),3.03(dd,J=12.9,6.9Hz,2H),2.81(d,J=10.0Hz,2H),2.61(dd,J=15.0,8.9Hz,2H),2.42(t,J=7.6Hz,2H),2.12-1.88(m,3H),1.76-1.54(m,8H)。

[1025] 2-(2-氯苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物90)

[1026] 

[1027] 化合物90(500MHz,甲醇-d_4)δ7.84-7.78(m,1H),7.57-7.51(m,1H),7.46-7.37(m,2H),7.20(d,J=7.3Hz,1H),6.41(d,J=7.3Hz,1H),4.97(s,1H),3.87-3.77(m,1H),3.42-3.36(m,2H),3.21(t,J=6.9Hz,2H),3.11-3.03(m,1H),2.98-2.80(m,2H),2.72(t,J=6.3Hz,2H),2.57(t,J=7.7Hz,2H),2.50-2.41(m,1H),2.09-1.79(m,8H)。

[1028] 2-(3-氯苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物91)

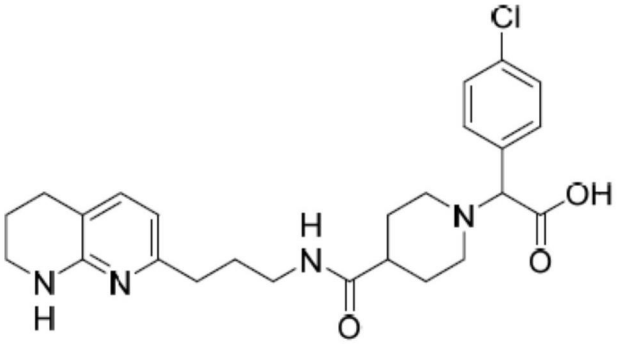
[1029] 

[1030] 化合物91 LC/MS A:100%纯度,UV=214nm,Rt=1.68min,ESI 471.3$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.67(s,1H),7.53-7.49(m,1H),7.47-7.40(m,2H),7.22(d,J=7.3Hz,1H),6.42(d,J=7.3Hz,1H),4.36(d,J=3.6Hz,1H),3.75-3.67(m,1H),3.42-3.38

(m,2H),3.21(t,J=6.9Hz,2H),3.09-3.00(m,1H),2.89-2.80(m,1H),2.72(t,J=6.3Hz,3H),2.57(t,J=7.7Hz,2H),2.47-2.37(m,1H),2.07-1.80(m,8H)。

[1031] 2-(4-氯苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物92)

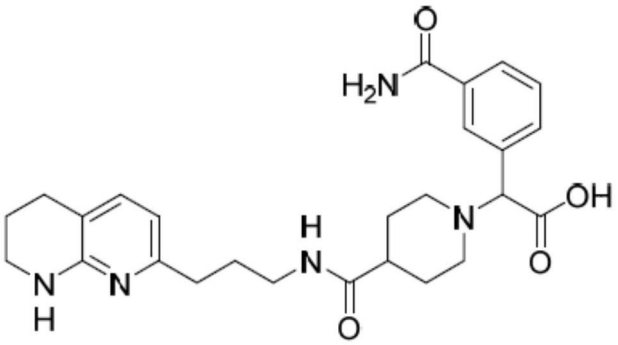
[1032]



[1033] 化合物92 LC/MS A:99%纯度,UV=214nm,Rt=1.52min,ESI 471.2$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.57(d,J=8.5Hz,2H),7.49-7.43(m,2H),7.19(d,J=7.3Hz,1H),6.41(d,J=7.3Hz,1H),4.40(s,1H),3.77-3.66(m,1H),3.41-3.37(m,2H),3.21(t,J=6.9Hz,2H),3.11-3.01(m,1H),2.94-2.83(m,1H),2.82-2.67(m,3H),2.56(t,J=7.6Hz,2H),2.48-2.38(m,1H),2.05-1.79(m,8H)。

[1034] 2-(3-氨甲酰基苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物93)

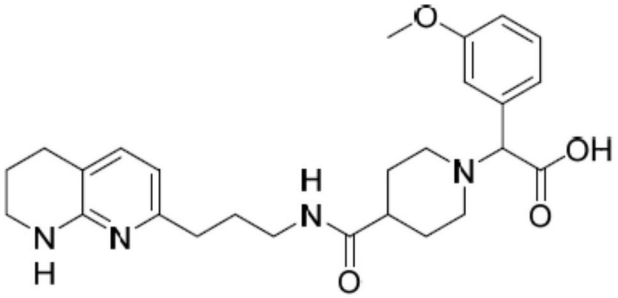
[1035]



[1036] 化合物93 LC/MS A:100%纯度,UV=214nm,Rt=1.09min,ESI 480.2$(M+H)^+$。^{1}H NMR(500MHz,甲醇-d_4)δ8.07(d,J=1.9Hz,1H),7.91(d,J=8.1Hz,1H),7.76(d,J=7.8Hz,1H),7.58-7.51(m,1H),7.18(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),4.42(s,1H),3.79-3.67(m,1H),3.42-3.37(m,2H),3.20(t,J=6.9Hz,2H),3.09-3.01(m,1H),2.91-2.82(m,1H),2.71(t,J=6.3Hz,3H),2.55(t,J=7.7Hz,2H),2.46-2.36(m,1H),2.08-1.80(m,8H)。

[1037] 2-(3-甲氧基苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物94)

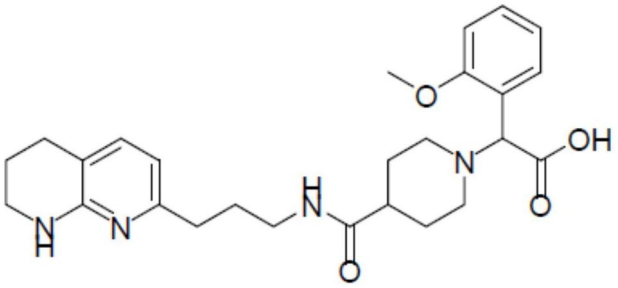
[1038]



[1039] 化合物94 LC/MS A:100%纯度,UV=214nm,Rt=1.50min,ESI 467.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.35(t,J=8.0Hz,1H),7.21-7.11(m,3H),7.00(dd,J=8.3,2.3Hz,1H),6.39(d,J=7.3Hz,1H),4.38(s,1H),3.75(s,1H),3.46-3.34(m,2H),3.20(t,J=6.9Hz,2H),3.06(s,1H),2.93(t,J=8.6Hz,1H),2.82(s,1H),2.71(t,J=6.3Hz,2H),2.60-2.51(m,2H),2.45(ddd,J=14.7,10.4,4.2Hz,1H),2.20-1.76(m,8H)。

[1040] 2-(2-甲氧基苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物95)

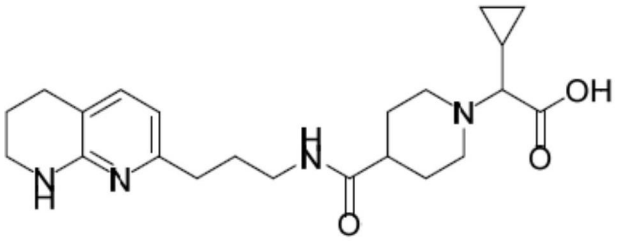
[1041]



[1042] 化合物95 LC/MS A:100%纯度,UV=214nm,Rt=1.49min,ESI 467.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.56(dd,J=7.7,1.5Hz,1H),7.50-7.43(m,1H),7.13(dd,J=9.7,8.2Hz,2H),7.05(t,J=7.4Hz,1H),6.38(d,J=7.3Hz,1H),4.97(s,1H),3.92(s,3H),3.43-3.34(m,2H),3.21(dd,J=15.7,8.8Hz,3H),3.02(d,J=3.3Hz,1H),2.72(dd,J=18.3,12.0Hz,2H),2.59-2.50(m,2H),2.45(s,1H),2.14-1.69(m,8H)。

[1043] 2-环丙基-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物96)

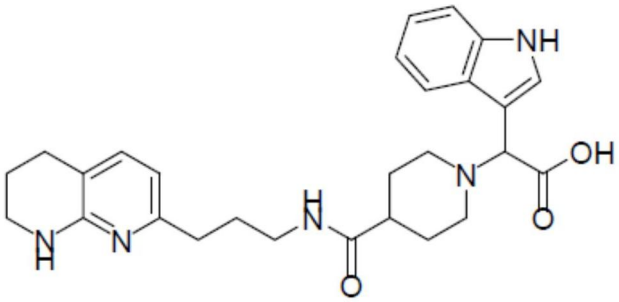
[1044]



[1045] 化合物96 LC/MS A:98%纯度,UV=214nm,Rt=1.42min,ESI 401.2(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.16(d,J=7.4Hz,1H),6.40(d,J=7.3Hz,1H),3.87(d,J=12.3Hz,1H),3.59(dd,J=10.2,6.0Hz,1H),3.42-3.37(m,2H),3.22(t,J=7.0Hz,2H),3.10-2.96(m,2H),2.84(d,J=9.5Hz,1H),2.71(t,J=6.3Hz,2H),2.58-2.53(m,2H),2.53-2.45(m,1H),2.10-1.97(m,4H),1.92-1.79(m,4H),1.18-1.07(m,1H),0.88-0.76(m,1H),0.76-0.64(m,2H),0.62-0.54(m,1H)。

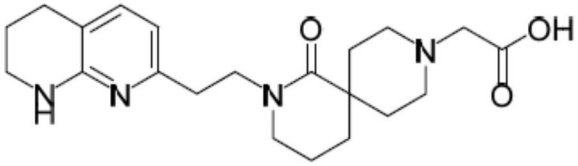
[1046] 2-(1H-吲哚-3-基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)

哌啶-1-基)乙酸(化合物97)

[1047] 

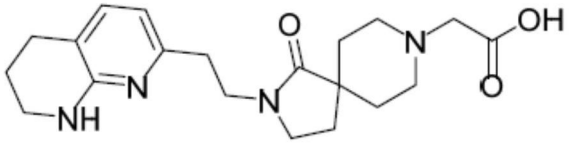
[1048] 化合物97 LC/MS A:100%纯度,UV=214nm,Rt=1.52min,ESI 476(M+H)$^{+}$。^{1}H NMR(500MHz,MeOD)δ7.78(d,J=7.9Hz,1H),7.54(s,1H),7.43(d,J=8.1Hz,1H),7.18(t,J=7.3Hz,1H),7.12(t,J=6.9Hz,2H),6.36(d,J=7.3Hz,1H),4.84(s,1H),3.69(s,1H),3.36(d,J=5.6Hz,3H),3.18(t,J=6.9Hz,2H),3.05(t,J=10.8Hz,1H),2.68(t,J=6.2Hz,3H),2.52(t,J=7.6Hz,2H),2.38(s,1H),1.86(ddt,J=21.9,14.3,11.8Hz,8H)。

[1049] 2-(1-氧代基-2-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-2,9-二氮杂螺[5.5]十一烷-9-基)乙酸(化合物98)

[1050] 

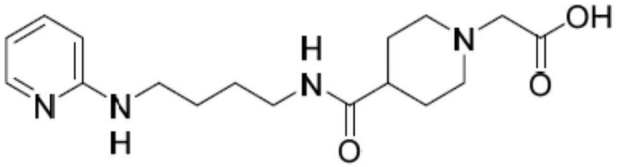
[1051] 化合物98 LC/MS A:100%纯度,UV=214nm,Rt=1.41min,ESI 387.2(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.30(d,J=7.3Hz,1H),6.47(d,J=7.3Hz,1H),3.70-3.57(m,4H),3.54(s,2H),3.48-3.41(m,2H),3.19(s,4H),2.83(t,J=6.9Hz,2H),2.76(t,J=6.2Hz,2H),2.13(br,2H),1.96-1.89(m,2H),1.84(s,2H),1.78-1.69(m,2H)。

[1052] 2-(1-氧代基-2-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-2,8-二氮杂螺[4.5]癸烷-8-基)乙酸(化合物99)

[1053] 

[1054] 化合物99 LC/MS A:100%纯度,UV=214nm,Rt=1.36min,ESI 373.0(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.14(d,J=7.3Hz,1H),6.41(d,J=7.3Hz,1H),3.59(m,6H),3.45-3.34(m,4H),3.18(s,2H),2.74(dt,J=12.4,6.5Hz,4H),2.00(d,J=6.8Hz,4H),1.91-1.81(m,2H),1.71(d,J=14.1Hz,2H)。

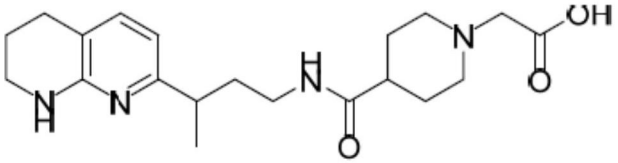
[1055] 2-(4-((4-(吡啶-2-基氨基)丁基)氨甲酰基)哌啶-1-基)乙酸(化合物100)

[1056] 

[1057] 化合物100LC/MS A:100%纯度,UV=214nm,Rt=1.30min,ESI 335.2(M+H)$^{+}$。^{1}H NMR(500MHz,MeOD)δ7.90(d,J=5.2Hz,1H),7.50(t,J=7.8Hz,1H),6.60(dd,J=12.3,

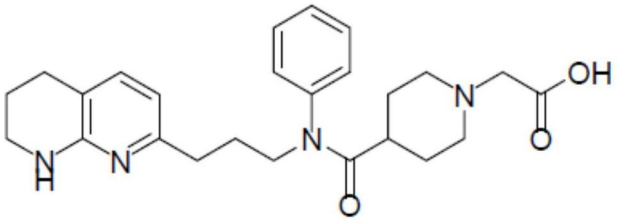
7.5Hz,2H),4.95(s,2H),3.74-3.58(m,4H),3.25(t,J=5.9Hz,2H),3.07(s,2H),2.57-2.46(m,1H),2.10-1.97(m,4H),1.64(s,4H)。

[1058] 2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)哌啶-1-基)乙酸(化合物101)

[1059] 

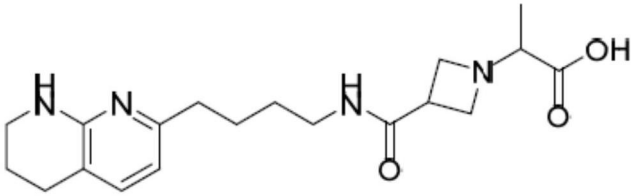
[1060] 化合物101 LC/MS B:100%纯度,UV=214nm,Rt=1.44min,ESI375(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ8.45(s,1H),7.47(d,J=7.4Hz,1H),6.57(d,J=7.4Hz,1H),3.71(t,J=11.2Hz,2H),3.64(s,2H),3.51-3.46(m,2H),3.23-3.17(m,2H),3.10(s,2H),2.86-2.77(m,3H),2.52(s,1H),2.09-2.01(m,4H),1.97-1.87(m,3H),1.82-1.79(m,1H),1.32(d,J=7.0Hz,3H)。

[1061] 2-(4-(苯基(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物102)

[1062] 

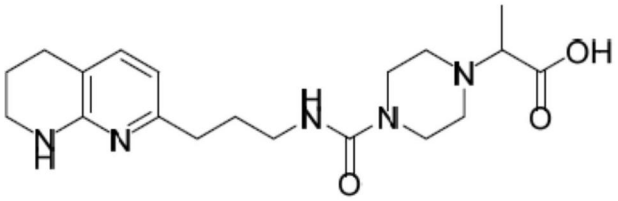
[1063] 化合物102 LC/MS A:100%纯度,UV=254nm,Rt=1.53min,ESI 437(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.53(dd,J=10.3,4.7Hz,2H),7.46(t,J=7.4Hz,1H),7.34(d,J=7.3Hz,2H),7.16(d,J=7.3Hz,1H),6.37(d,J=7.3Hz,1H),3.77-3.72(m,2H),3.56(d,J=12.6Hz,2H),3.48(s,2H),3.41-3.36(m,2H),2.81-2.68(m,4H),2.56-2.49(m,3H),2.06(dd,J=23.5,11.1Hz,2H),1.94-1.84(m,6H)。

[1064] 2-(3-((4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨甲酰基)氮杂环丁烷-1-基)丙酸(化合物103)

[1065] 

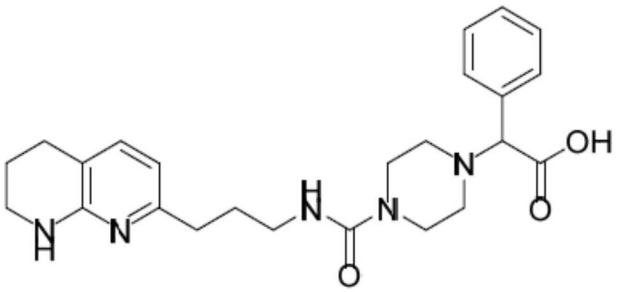
[1066] 化合物103 LC/MS A:100%纯度,UV=214nm,Rt=1.51min,ESI 361.3(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.16(d,J=7.3Hz,1H),6.38(d,J=7.3Hz,1H),4.36-4.15(m,2H),4.09(t,J=9.0Hz,2H),3.74(q,J=7.0Hz,1H),3.50(dt,J=16.2,8.1Hz,1H),3.44-3.36(m,2H),3.25(t,J=6.9Hz,2H),2.72(t,J=6.2Hz,2H),2.55(t,J=7.6Hz,2H),1.95-1.78(m,2H),1.75-1.60(m,2H),1.56-1.39(m,2H),1.39(d,J=7.1Hz,3H)。

[1067] 2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌嗪-1-基)丙酸(化合物104)

[1068] 

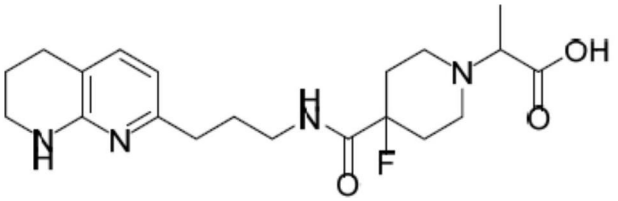
[1069] 化合物104 LC/MS A:100%纯度,UV=214nm,Rt=1.34min,ESI 376(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ8.50(s,1H),7.50(d,J=7.3Hz,1H),6.57(d,J=7.3Hz,1H),3.66(m,5H),3.52-3.44(m,2H),3.41-3.33(m,4H),3.28(t,J=6.3Hz,2H),2.80(t,J=6.1Hz,2H),2.75-2.66(m,2H),2.00-1.90(m,2H),1.91-1.81(m,2H),1.55(d,J=7.2Hz,3H)。

[1070] 2-苯基-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌嗪-1-基)乙酸(化合物105)

[1071] 

[1072] 化合物105 LC/MS A:100%纯度,UV=214nm,Rt=1.42min,ESI 438(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.55(d,J=8.2Hz,2H),7.42-7.29(m,4H),6.49(d,J=7.3Hz,1H),4.01(s,1H),3.55-3.44(m,3H),3.43-3.38(m,3H),3.22(m,2H),2.79(m,4H),2.63(m,4H),1.95-1.79(m,4H).

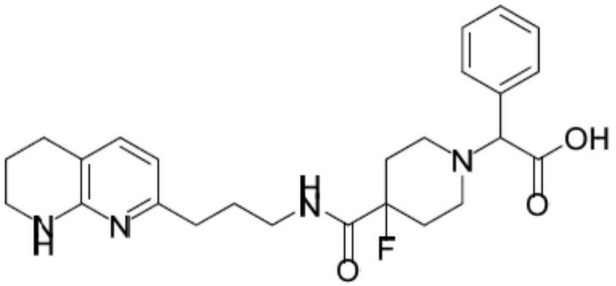
[1073] 2-(4-氟-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(化合物106)

[1074] 

[1075] 化合物106 LC/MS A:100%纯度,UV=214nm,Rt=1.41min,ESI 393.2(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.17(d,J=7.3Hz,1H),6.41(d,J=7.4Hz,1H),3.56(q,J=7.1Hz,1H),3.52-3.44(m,2H),3.41-3.36(m,2H),3.28(t,J=7.0Hz,2H),3.24-3.09(m,2H),2.72(t,J=6.0Hz,2H),2.57(t,J=7.7Hz,2H),2.53-2.38(m,2H),2.15-2.03(m,2H),1.93-1.83(m,4H),1.51(d,J=7.1Hz,3H)。

[1076] 2-(4-氟-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)-2-苯基乙酸(化合物107)

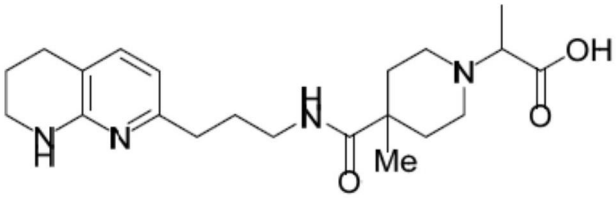
[1077]



[1078] 化合物107 LC/MS A:100%纯度,UV=214nm,Rt=1.50min,ESI 455.3(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.63-7.54(m,2H),7.46-7.37(m,3H),7.24(d,J=7.4Hz,1H),6.43(d,J=7.3Hz,1H),4.34(s,1H),3.67-3.57(m,1H),3.41-3.37(m,2H),3.26(t,J=6.9Hz,2H),3.06-2.96(m,1H),2.94-2.87(m,1H),2.85-2.75(m,1H),2.72(t,J=6.3Hz,2H),2.58(t,J=7.7Hz,2H),2.54-2.30(m,2H),2.09-2.00(m,1H),1.95-1.81(m,5H)。

[1079] 2-(4-甲基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(化合物108)

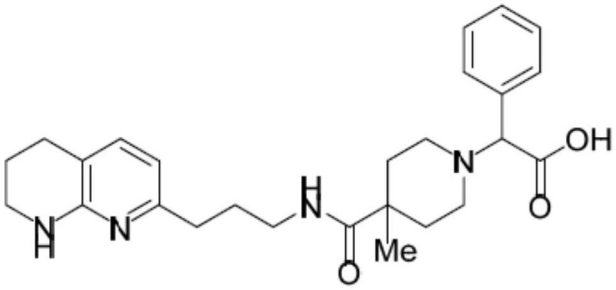
[1080]



[1081] 化合物108 LC/MS A:100%纯度,UV=214nm,Rt=1.41min,ESI 389.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.23(d,J=7.3Hz,1H),6.44(d,J=7.3Hz,1H),3.52(d,J=7.2Hz,1H),3.44-3.38(m,2H),3.31-3.15(m,6H),2.73(t,J=6.2Hz,2H),2.64-2.56(m,2H),2.31(d,J=12.2Hz,2H),1.88(ddd,J=22.2,13.4,6.9Hz,4H),1.73(ddd,J=19.4,13.3,3.9Hz,2H),1.47(d,J=7.2Hz,3H),1.24(s,3H)。

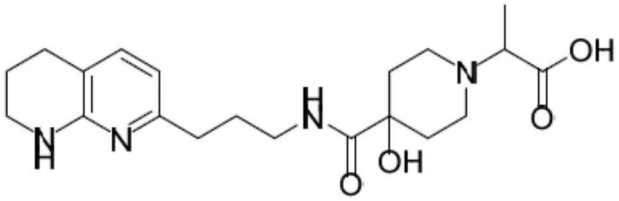
[1082] 2-(4-甲基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)-2-苯基乙酸(化合物109)

[1083]



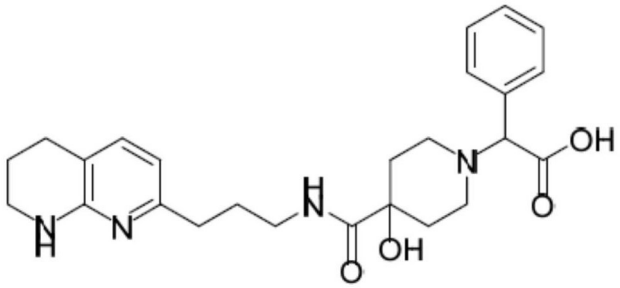
[1084] 化合物109 LC/MS A:100%纯度,UV=214nm,Rt=1.49min,ESI 451.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.55(dd,J=7.3,2.1Hz,2H),7.47-7.37(m,3H),7.22(d,J=7.3Hz,1H),6.43(d,J=7.3Hz,1H),4.51(s,1H),3.43-3.37(m,2H),3.26(td,J=6.6,3.3Hz,3H),2.99(s,3H),2.73(t,J=6.2Hz,2H),2.58(dd,J=14.6,7.2Hz,2H),2.24(d,J=13.1Hz,2H),1.96-1.65(m,6H),1.22(s,3H)。

[1085] 2-(4-羟基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(化合物110)

[1086] 

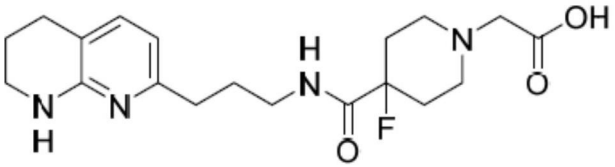
[1087] 化合物110LC/MS A:100%纯度,UV=214nm,Rt=1.38min,ESI 391(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.15(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),3.62(q,J=7.1Hz,1H),3.54-3.46(m,2H),3.43-3.37(m,2H),3.33-3.23(m,4H),2.72(t,J=6.3Hz,2H),2.57(t,J=7.6Hz,2H),2.40(td,J=14.6,4.2Hz,2H),1.92-1.80(m,6H),1.54(d,J=7.1Hz,3H)。

[1088] 2-(4-羟基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)-2-苯基乙酸(化合物111)

[1089] 

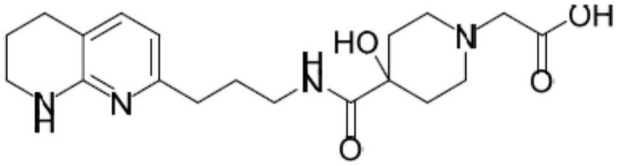
[1090] (化合物111)LC/MS A:98%纯度,UV=214nm,Rt=1.46min,ESI 453(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.61(dd,J=6.6,2.9Hz,2H),7.48-7.42(m,3H),7.15(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.53(s,1H),3.71(s,1H),3.42-3.36(m,2H),3.24(t,J=6.9Hz,3H),3.01(d,J=54.4Hz,2H),2.71(t,J=6.3Hz,2H),2.55(t,J=7.5Hz,2H),2.45(t,J=12.3Hz,1H),2.34(dd,J=19.3,8.9Hz,1H),1.90-1.78(m,5H),1.69(d,J=12.8Hz,1H)。

[1091] 2-(4-氟-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物112)

[1092] 

[1093] 化合物112 LC/MS A:100%纯度,UV=214nm,Rt=1.40min,ESI 379.1(M+H)$^+$。^{1}H NMR(500MHz,甲醇-d_4)δ7.19(d,J=7.3Hz,1H),6.42(d,J=7.4Hz,1H),3.48(s,2H),3.46-3.38(m,4H),3.28(t,J=6.9Hz,2H),3.05-2.95(m,2H),2.72(t,J=6.2Hz,2H),2.57(t,J=7.6Hz,2H),2.52-2.36(m,2H),2.06-1.97(m,2H),1.92-1.83(m,4H)。

[1094] 2-(4-羟基-4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)乙酸(化合物113)

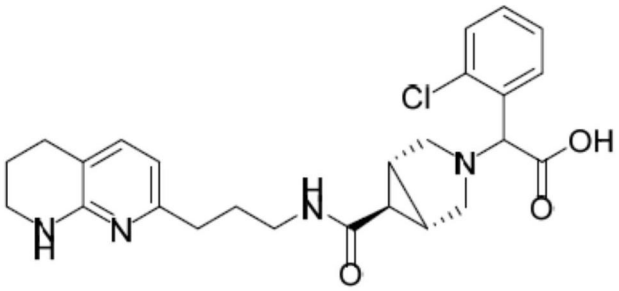
[1095] 

[1096] 化合物113 LC/MS A:100%纯度,UV=214nm,Rt=1.38min,ESI 377(M+H)$^+$。^{1}H NMR

(500MHz,MeOD)δ7.15(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),3.64(s,2H),3.56(d,J=12.4Hz,2H),3.42-3.37(m,2H),3.27(dd,J=16.8,9.9Hz,4H),2.72(t,J=6.3Hz,2H),2.59-2.53(m,2H),2.39(td,J=14.5,4.3Hz,2H),1.92-1.78(m,6H)。

[1097] 2-(2-氯苯基)-2-((1R,5S,6r)-6-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)-3-氮杂二环[3.1.0]己烷-3-基)乙酸(化合物114)

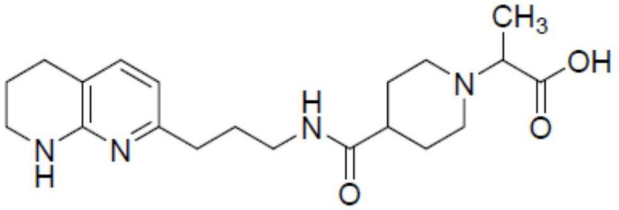
[1098]



[1099] 化合物114 LC/MS A:100%纯度,UV=214nm,Rt=1.51min,ESI 469$(M+H)^+$。^{1}H NMR (500MHz,MeOD)δ7.76-7.70(m,1H),7.42(d,J=7.5Hz,1H),7.37(d,J=7.2Hz,1H),7.34-7.25(m,2H),6.51(d,J=7.3Hz,1H),4.72(s,1H),3.43(dd,J=12.2,7.0Hz,3H),3.22(t,J=6.7Hz,2H),2.95(d,J=7.0Hz,1H),2.87(d,J=9.8Hz,1H),2.76(t,J=6.1Hz,3H),2.63(t,J=7.5Hz,2H),2.09(s,1H),2.03-1.97(m,1H),1.92(dt,J=12.0,5.8Hz,3H),1.85(dd,J=14.4,7.2Hz,2H)。

[1100] 2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(化合物115)

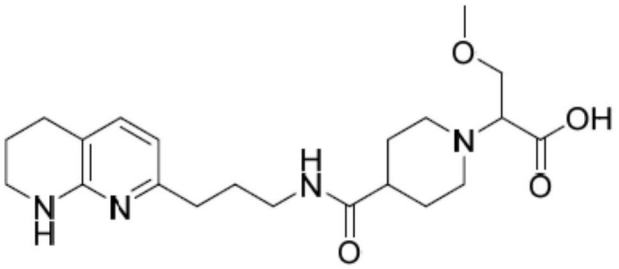
[1101]



[1102] 化合物115 LC/MS F:97%纯度,UV 254nm,Rt=1.896,ESI 375.2(M+H)。^{1}H NMR (400MHz,DMSO-d6)δ7.8-7.75(m,1H),7.03(d,J=7.2Hz,1H),6.34(bs,1H),6.26(d,1H),3.27-3.21(m,3H),3.11-2.99(m,4H),2.62-2.53(m,3H),2.41(m,2H),2.16(m,3H),1.78-1.59(m,8H),1.21(d,J=7.2Hz,3H)

[1103] 3-甲氧基-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(化合物116)

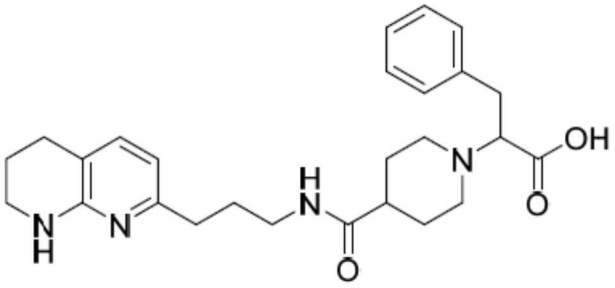
[1104]



[1105] 化合物116 LC/MS F:96%纯度,UV 254nm,Rt=1.842,ESI 437.2(M+H)。^{1}H NMR (400MHz,DMSO-d6)δ7.72(t,1H),7.02(d,1H),6.28(bs,1H),6.24(d,J=7.24,1H),3.68-3.64(m,1H),3.61-3.57(m,1H),3.34(t,1H)3.26-3.21(q,5H),3.05-2.98(m,4H),2.62-

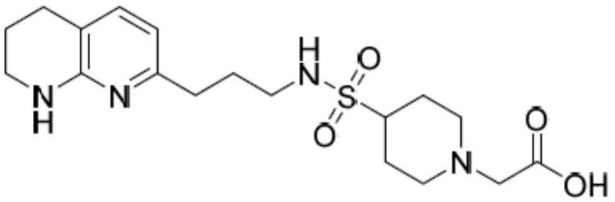
2.55(m,3H),2.43-2.37(m,2H),2.17-2.09(m,2H),1.79-1.59(m,8H)

[1106] 3-苯基-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)哌啶-1-基)丙酸(化合物117)

[1107] 

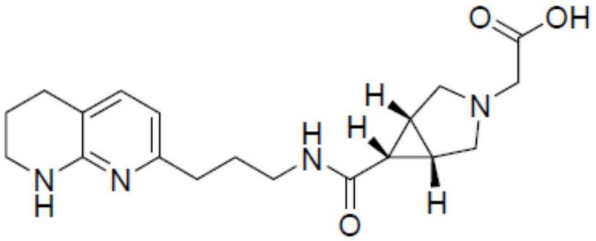
[1108] 化合物117 LC/MS F:96%纯度,UV 254nm,Rt=3.123min,ESI451.2(M+H)。^{1}H NMR ^{1}H NMR(400MHz,DMSO-d_6)δ7.66(t,J=5.6Hz,1H),7.31-7.12(m,4H),6.95(d,J=7.2Hz,1H),6.21-6.14(m,2H),3.72(dd,J=10.5,5.3Hz,2H),3.20-3.12(m,2H),3.08-2.90(m,5H),2.86(m,1H),2.53(t,J=6.3Hz,2H),2.37(t,J=6.5Hz,2H),2.14-1.87(m,3H),1.74-1.35(m,8H)

[1109] 2-(4-(N-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨磺酰基)哌啶-1-基)乙酸(化合物118)

[1110] 

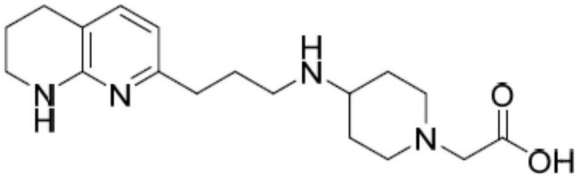
[1111] 化合物118 LC/MS F:96%纯度,UV 254nm ESI 397.2(M+H)。^{1}H NMR(400MHz,DMSO-d_6)δ7.04(t,J=5.7Hz,1H),6.96(d,J=7.2Hz,1H),6.22-6.15(m,2H),3.21-3.12(m,2H),3.09(s,2H),2.99-2.78(m,5H),2.53(t,J=6.3Hz,2H),2.42-2.33(m,2H),2.29-2.18(m,2H),1.85(m,2H),1.71-1.52(m,6H)

[1112] 2-((1R,5S,6s)-6-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)-3-氮杂二环[3.1.0]己烷-3-基)乙酸(化合物119)

[1113] 

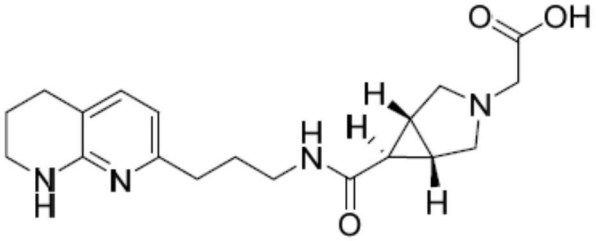
[1114] 化合物119 LC/MS F:95%纯度,UV 254nm,Rt=2.78min,ESI 359.2(M+H)。^{1}H NMR(400MHz,DMSO-d6)δ8.67(t,J=5.5Hz,1H),7.05-6.98(d,J=7.2Hz,1H),6.67(bs,1H),6.23(d,J=7.2Hz,1H),3.38(d,J=10.7Hz,2H),3.28(s,2H)3.22-3.14(m,2H),3.09-2.92(m,4H),2.54(t,J=6.3Hz,2H),2.43-2.28(m,2H),1.93-1.85(m,2H),1.74-1.54(m,5H)。

[1115] 2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨基)哌啶-1-基)乙酸(化合物120)

[1116] 

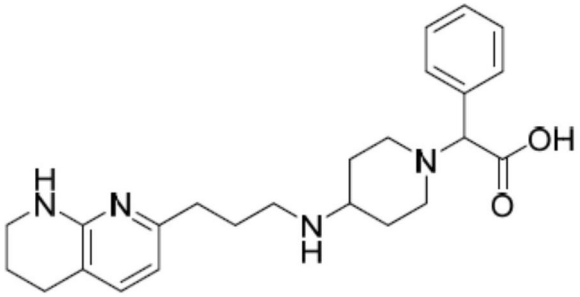
[1117] 化合物120LC/MS F:95%纯度,UV 254nm ESI 333.2(M+H)。^{1}H NMR(400MHz,DMSO-d_6)δ7.04(d,J=7.3Hz,1H),6.31-6.22(m,2H),3.26-3.22(m,2H),3.15(s,2H),3.09-3.02(m,2H),2.74-2.65(m,2H),2.61(t,J=6.3Hz,2H),2.50-2.42(m,3H),1.93-1.84(m,2H),1.83-1.7(m,4H),1.56-1.42(m,2H)。

[1118] 2-((1R,5S,6r)-6-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰基)-3-氮杂二环[3.1.0]己烷-3-基)乙酸(化合物121)

[1119] 

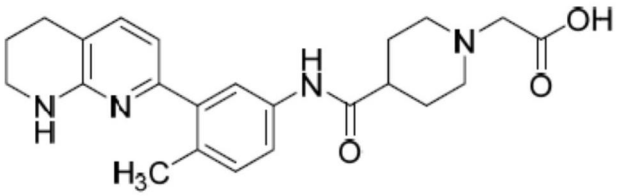
[1120] 化合物121 LC/MS F:95%纯度,UV 254nm,Rt=2.586,ESI 359.2(M+H)。^{1}H NMR(400MHz,D_2O)δ7.46(d,J=7.4Hz,1H),6.52(d,J=7.3Hz,1H),3.72(m,4H),3.52(bs,2H),3.43-3.35(m,2H),3.18(t,J=6.6Hz,2H),2.71(t,J=6.3Hz,2H),2.63(t,J=7.4Hz,2H),2.19(t,J=3.1Hz,2H),1.91-1.81(m,4H),1.78(t,J=3.4Hz,1H)。

[1121] 2-苯基-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨基)哌啶-1-基)乙酸(化合物122)

[1122] 

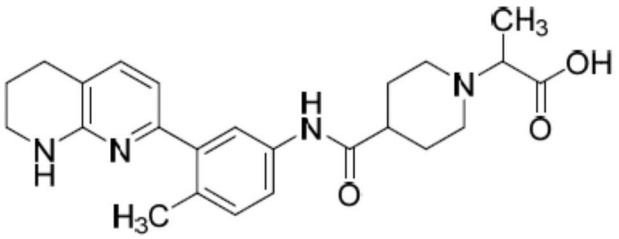
[1123] 化合物122 LC/MS F:98%纯度,UV 254nm,Rt=1.315min,ESI409.3(M+H)。^{1}H NMR(400MHz,DMSO-d_6)δ7.45-7.28(m,5H),7.06(d,J=7.3Hz,1H),6.33-6.26(m,2H),4.03(s,1H),3.3-3.22(m,2H),3.07-3.01(m,1H),2.96-2.81(m,3H),2.78-2.73(m,1H),2.62(t,J=6.2Hz,2H),2.48(t,J=6.2Hz,2H),2.27-2.2(m,1H),2.09-1.86(m,5H),1.82-1.71(m,2H),1.68-1.54(m,2H)。

[1124] 2-(4-((4-甲基-3-(5,6,7,8-四氢-1,8-萘啶-2-基)苯基)氨甲酰基)哌啶-1-基)乙酸(化合物123)

[1125] 

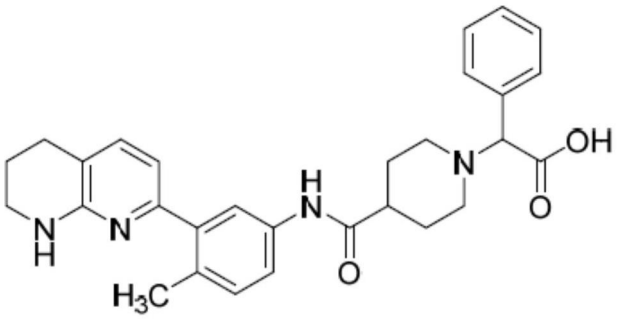
[1126] 化合物123 LC/MS F:97%纯度,UV 254nm,Rt=3.218min,ESI409.2(M+H)。^{1}H NMR (400MHz,DMSO-d6)δ9.84(s,1H),7.57(d,J=2.3Hz,1H),7.45(dd,J=8.2,2.3Hz,1H),7.23-7.16(m,1H),7.12(d,J=8.3Hz,1H),6.45(d,J=7.3Hz,1H),6.39(s,1H),3.33-3.26(m,2H),3.22(s,2H),3.19-3.13(m,2H),2.69(t,J=6.2Hz,2H),2.55-2.51(m,J=3.6Hz,2H),2.43-2.35(m,1H),2.24(s,3H),1.86-1.74(m,6H)

[1127] 2-(4-((4-甲基-3-(5,6,7,8-四氢-1,8-萘啶-2-基)苯基)氨甲酰基)哌啶-1-基)丙酸(化合物124)

[1128] 

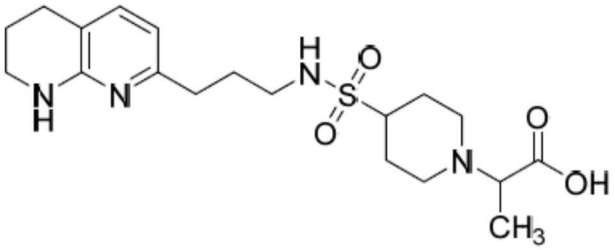
[1129] 化合物124 LC/MS F:99%纯度,UV 254nm,Rt=3.232min,ESI423.2(M+H)。^{1}H NMR (400MHz,DMSO-d6)δ9.80(s,1H),7.57(d,J=2.4Hz,1H),7.44(dd,J=8.2,2.4Hz,1H),7.20(d,J=7.4Hz,1H),7.12(d,J=8.2Hz,1H),6.45(d,J=7.3Hz,1H),6.38(s,1H),3.30-3.20(m,3H),3.06(m,2H),2.69(t,J=6.2Hz,2H),2.59-2.49(m,2H),2.43-2.31(m,2H),2.24(s,3H),1.86-1.65(m,6H),1.21(d,J=7.0Hz,3H)。

[1130] 2-(4-((4-甲基-3-(5,6,7,8-四氢-1,8-萘啶-2-基)苯基)氨甲酰基)哌啶-1-基)-2-苯基乙酸(化合物125)

[1131] 

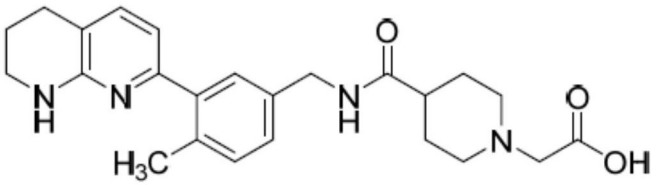
[1132] 化合物125 LC/MS F:95%纯度,UV 254nm,Rt=3.399min,ESI485.2(M+H)。^{1}H NMR (400MHz,DMSO-d6)δ9.80(s,1H),7.56(d,J=2.3Hz,1H),7.48-7.25(m,6H),7.19(d,J=7.4Hz,1H),7.11(d,J=8.3Hz,1H),6.45(d,J=7.2Hz,1H),6.38(bs,1H),3.31-3.26(s,4H),3.22-3.18(m,1H),2.79-3.72(m,1H),2.69(t,J=6.3Hz,2H),2.43-2.32(m,1H),2.25-2.13(m,4H),1.84-1.70(m,6H)。

[1133] 2-(4-(N-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨磺酰基)哌啶-1-基)丙酸(化合物126)

[1134] 

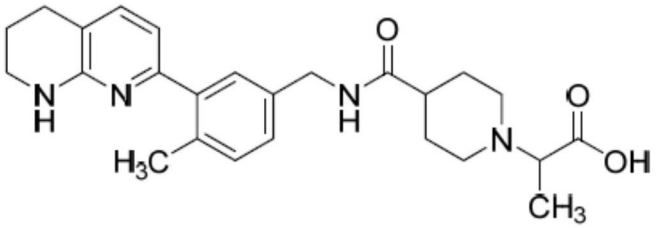
[1135] 化合物126 LC/MS F:99%纯度,UV 254nm,Rt=2.929min,ESI411.2(M+H)。^{1}H NMR (400MHz,DMSO-d6)δ7.56-7.49(d,7.3Hz,1H),7.36(t,J=5.8Hz,1H),6.57(d,J=7.3Hz,1H),3.71-3.61(m,1H),3.42-3.36(m,2H),3.31-3.15(m,3H),3.01-2.95(m,2H),2.9-2.8(m,2H),2.75-2.64(m,4H),2.12-2.03(m,2H),1.94-1.75(m,6H),1.34(d,J=7.2,3H)。

[1136] 2-(4-((4-甲基-3-(5,6,7,8-四氢-1,8-萘啶-2-基)苄基)氨甲酰基)哌啶-1-基)乙酸(化合物127)

[1137] 

[1138] 化合物127 LC/MS F:97%纯度,UV 254nm,Rt=3.216min,ESI423.2(M+H)。^{1}H NMR (400MHz,DMSO-d6)δ8.30(t,J=5.9Hz,1H),7.23-7.12(m,3H),7.08(dd,J=7.8,1.9Hz,1H),6.45(d,J=7.3Hz,1H),6.38(s,1H),4.23(d,J=5.9Hz,2H),3.27(m,2H),3.17(s,2H),3.14-3.06(m,2H),2.69(t,J=6.3Hz,2H),2.50-2.42(m,2H),2.2-2.17(m,4H),1.84-1.67(m,6H)。

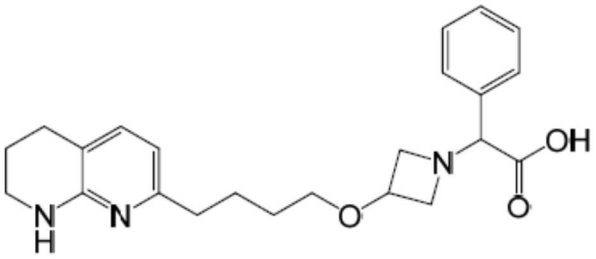
[1139] 2-(4-((4-甲基-3-(5,6,7,8-四氢-1,8-萘啶-2-基)苄基)氨甲酰基)哌啶-1-基)丙酸(化合物128)

[1140] 

[1141] 化合物128 LC/MS F:99%纯度,UV 254nm,Rt=3.226min,ESI437.2(M+H)。^{1}H NMR (400MHz,DMSO-d_6)δ8.29(t,J=5.9Hz,1H),7.23-7.12(m,3H),7.08(dd,J=7.8,1.9Hz,1H),6.48-6.38(m,2H),4.23(d,J=5.9Hz,2H),3.33-3.21(m,3H),3.05(t,J=13.3Hz,2H),2.69(t,J=6.3Hz,2H),2.58-2.51(m,2H),2.28-2.21(m,4H),1.83-1.65(m,6H),1.20(d,J=7.1Hz,3H)。

[1142] 根据一般程序,使用与用于制备化合物1至28和129至133使用的那些类似的方法制备化合物134至201。

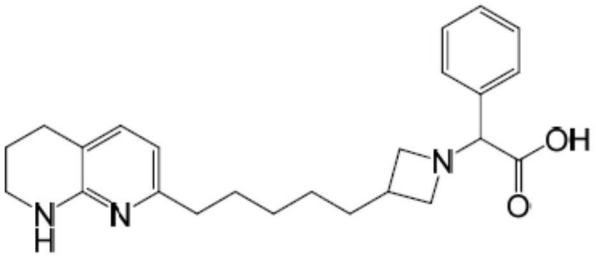
[1143] 2-苯基-2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)氮杂环丁烷-1-基)乙酸(对映异构化合物134-E1和134-E2)

[1144] 

[1145] 化合物134-E1 LC/MS ESI 396(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.56-7.35(m,5H),7.15(d,J=7.3Hz,1H),6.37(d,J=7.3Hz,1H),4.65(s,1H),4.30-4.28(m,2H),3.93-3.91(m,2H),3.75-3.71(m,1H),3.47-3.36(m,4H),2.70(t,J=6.3Hz,2H),2.54(t,J=7.5Hz,2H),1.96-1.81(m,2H),1.76-1.64(m,2H),1.59-1.55(m,2H)。手性SFC B(30%MeOH):ee 100%,Rt=1.06min。

[1146] 化合物134-E2 LC/MS ESI 396(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.56-7.35(m,5H),7.15(d,J=7.3Hz,1H),6.37(d,J=7.3Hz,1H),4.65(s,1H),4.30-4.28(m,2H),3.93-3.91(m,2H),3.75-3.71(m,1H),3.47-3.36(m,4H),2.70(t,J=6.3Hz,2H),2.54(t,J=7.5Hz,2H),1.96-1.81(m,2H),1.76-1.64(m,2H),1.59-1.55(m,2H)。手性SFC B(30%MeOH):ee 99.5%,Rt=2.58min。

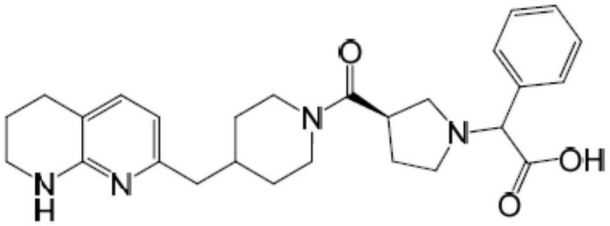
[1147] 2-苯基-2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)氮杂环丁烷-1-基)乙酸(对映异构化合物135-E1和135-E2

[1148] 

[1149] 化合物135-E1 LC/MS ESI 394.2(M+H)$^{+}$。^{1}H NMR(400MHz,MeOD)δ7.51-7.41(m,5H),7.11(d,J=7.2Hz,1H),6.34(d,J=7.2Hz,1H),4.67(s,1H),4.22(s,1H),3.77-3.33(m,5H),2.79-2.68(m,3H),2.49(t,J=7.6Hz,2H),1.92-1.84(m,2H),1.66-1.58(m,4H),1.34-1.22(m,4H)。手性SFC A(40%MeOH):ee 98%,Rt=1.96min。

[1150] 化合物135-E2 LC/MS ESI 394.2(M+H)$^{+}$。^{1}H NMR(400MHz,MeODδ7.40-7.31(m,5H),7.003(d,J=7.2Hz,1H),6.231(d,J=7.2Hz,1H),4.55(s,1H),4.10(s,1H),3.63-3.20(m,5H),2.68-2.56(m,3H),2.38(t,J=7.6Hz,2H),1.80-1.73(m,2H),1.55-1.47(m,4H),1.22-1.11(m,4H)。手性SFC A(40%MeOH):ee98%,Rt=3.63min。

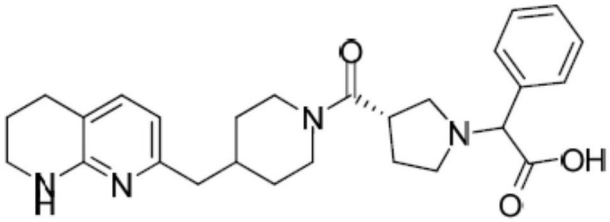
[1151] 2-苯基-2-((R)-3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)吡咯烷-1-基)乙酸(非对映异构化合物136-E1和136-E2)

[1152] 

[1153] 化合物136-E1 LC/MS ESI 463.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.59-7.56(m,2H),7.44-7.43(m,3H),7.12(d,J=7.3Hz,1H),6.35(m,J=5.5Hz,1H),4.46(m,2H),3.94(d,J=13.5Hz,1H),3.67(m,2H),3.39-3.35(m,3H),3.09-3.02(m,3H),2.69(m,3H),2.46(m,2H),2.43(m,1H),2.11-2.09(m,1H),1.96-1.83(m,3H),1.84-1.65(m,2H),1.19-1.09(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=2.16min。

[1154] 化合物136-E2 LC/MS ESI 463.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.59-7.56(m,2H),7.44-7.43(m,3H),7.12(d,J=7.3Hz,1H),6.35(m,J=5.5Hz,1H),4.46(m,2H),3.94(d,J=13.5Hz,1H),3.67(m,2H),3.39-3.35(m,3H),3.09-3.02(m,3H),2.69(m,3H),2.46(m,2H),2.43(m,1H),2.11-2.09(m,1H),1.96-1.83(m,3H),1.84-1.65(m,2H),1.19-1.09(m,2H)。手性SFC A(45%MeOH):ee 97%,Rt=3.68min。

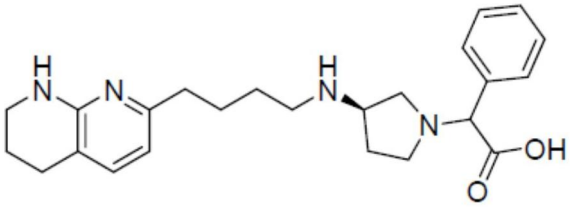
[1155] 2-苯基-2-((S)-3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)吡咯烷-1-基)乙酸(非对映异构化合物137-E1和137-E2)

[1156] 

[1157] 化合物137-E1 LC/MS ESI 463.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.59-7.52(m,2H),7.45-7.37(m,3H),7.12(d,J=7.3Hz,1H),6.35(t,J=5.5Hz,1H),4.46(d,J=13.8Hz,2H),3.91(d,J=13.5Hz,1H),3.54(s,3H),3.39-3.35(m,2H),3.09-3.02(m,3H),2.69(t,J=6.2Hz,2H),2.64-2.60(m,1H),2.43(t,J=7.1Hz,2H),2.30(d,J=6.7Hz,1H),2.11-2.09(m,1H),1.96-1.83(m,3H),1.73-1.65(m,2H),1.20-1.04(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=2.41min。

[1158] 化合物137-E2 LC/MS ESI 463.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.59-7.52(m,2H),7.46-7.38(m,3H),7.13(d,J=7.1Hz,1H),6.33(d,J=7.3Hz,1H),4.59(s,1H),4.46(d,J=12.3Hz,1H),3.92(d,J=13.4Hz,1H),3.63(s,2H),3.39-3.35(m,3H),3.16(br,1H),3.10-3.00(m,2H),2.69(t,J=6.3Hz,2H),2.61(t,J=13.3Hz,1H),2.44(d,J=7.1Hz,2H),2.28(d,J=18.9Hz,1H),2.11-2.00(m,1H),1.92(s,1H),1.89-1.84(m,2H),1.73-1.65(m,2H),1.20-1.04(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=3.43min。

[1159] 2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基氨基)吡咯烷-1-基)乙酸(非对映异构化合物138-E1和138-E2)

[1160] 

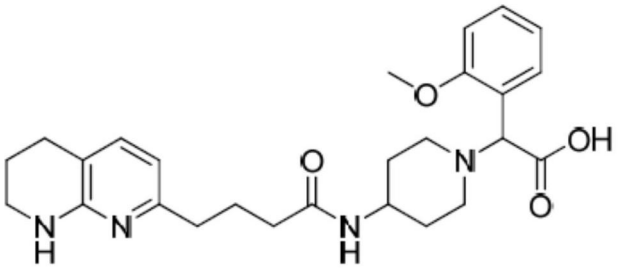
[1161] 化合物138-E1 LC/MS ESI 409.2(M+H)$^+$,^{1}H NMR(500MHz,MeOD)δ7.50(d,J=6.9Hz,2H),7.34-7.29(m,3H),7.18(d,J=7.3Hz,1H),6.41(d,J=7.3Hz,1H),3.86(s,1H),3.56(s,1H),3.42-3.38(m,2H),3.32-3.26(m,1H),2.97-2.90(m,1H),2.85-2.80(m,1H),

2.75-2.69(m,3H),2.59(t,J=7.1Hz,2H),2.37-2.30(m,2H),2.25-2.20(m,1H),2.09-2.07(m,2H),2.01-1.94(m,1H),1.92-1.86(m,2H),1.77-1.66(m,4H)。手性SFC F(45%MeOH):ee 100%,Rt=3.6min。

[1162] 化合物138-E2 LC/MS ESI 409.2$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.50(d,J=6.9Hz,2H),7.34-7.30(m,3H),7.18(d,J=7.3Hz,1H),6.43(d,J=7.3Hz,1H),3.86(s,1H),3.56(s,1H),3.45-3.38(m,2H),3.36-3.26(m,1H),2.98-2.90(m,1H),2.83-2.80(m,1H),2.75-2.69(m,3H),2.59(t,J=7.1Hz,2H),2.35-2.30(m,2H),2.24-2.20(m,1H),2.08-2.07(m,2H),2.02-1.94(m,1H),1.93-1.86(m,2H),1.79-1.66(m,4H)。手性SFC F(45%MeOH):ee 100%,Rt=5.6min。

[1163] 2-(2-甲氧基苯基)-2-(4-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)哌啶-1-基)乙酸(对映异构化合物139-E1和139-E2)

[1164]

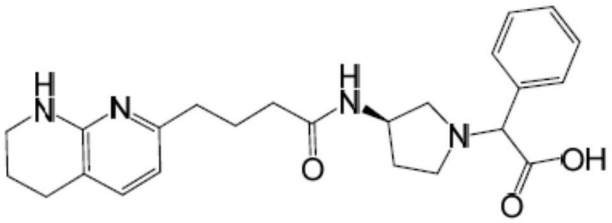


[1165] 化合物139-E1 LC/MS ESI 467.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.56(d,J=7.7Hz,1H),7.47-7.42(m,1H),7.15-7.11(m,2H),7.04(t,J=7.5Hz,1H),6.37(d,J=7.3Hz,1H),4.97(s,1H),3.92(s,3H),3.89(s,1H),3.72(br,1H),3.39(t,J=6Hz,2H),3.17(s,1H),3.09(t,J=11.2Hz,2H),2.71(t,J=6.2Hz,2H),2.53(t,J=7.5Hz,2H),2.20(t,J=7.5Hz,2H),2.06-2.02(m,2H),1.95-1.84(m,6H)。手性SFC A(45%MeOH):ee 100%,Rt=2.35min。

[1166] 化合物139-E2 LC/MS ESI 467.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.56(dd,J=7.6,1H),7.47-7.41(m,1H),7.15-7.11(m,2H),7.04(t,J=7.5Hz,1H),6.37(d,J=7.3Hz,1H),4.97(s,1H),3.92(s,3H),3.88(s,1H),3.71(br,1H),3.39(t,J=6Hz,2H),3.16(s,1H),3.08(t,J=11.3Hz,2H),2.71(t,J=6.3Hz,2H),2.53(t,J=7.6Hz,2H),2.20(t,J=7.5Hz,2H),2.05(t,J=16.2Hz,2H),1.95-1.76(m,6H)。手性SFC A(45%MeOH):ee 100%,Rt=3.03min。

[1167] 2-苯基-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁酰氨基)吡咯烷-1-基)乙酸(非对映异构化合物140-E1和140-E2)

[1168]



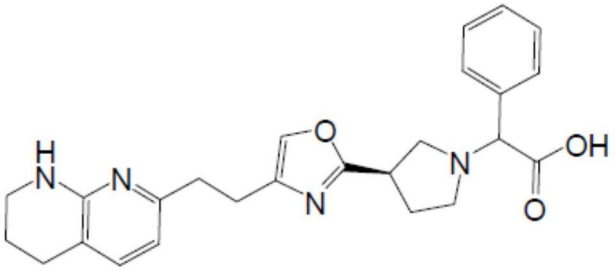
[1169] 化合物140-E1 LC/MS ESI 423.2$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.55(m,2H),7.43-7.39(m,3H),7.24(d,J=9.0Hz,1H),6.42(d,J=7.3Hz,1H),4.47(s,1H),4.33(s,1H),3.60-3.44(m,4H),2.99(s,2H),2.74-2.71(t,J=15.5Hz,2H),2.59-2.55(t,J=

19.3Hz,2H),2.30-2.20(m,3H),2.04-1.85(m,5H)。手性SFC A(45%MeOH):ee 100%,Rt=2.15min。

[1170] 化合物140-E2 LC/MS ESI 423.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.55(m,2H),7.43-7.39(m,3H),7.24(d,J=9.0Hz,1H),6.42(d,J=7.3Hz,1H),4.47(s,1H),4.33(s,1H),3.60-3.44(m,4H),2.99(s,2H),2.74-2.71(t,J=15.5Hz,2H),2.59-2.55(t,J=19.3Hz,2H),2.30-2.20(m,3H),2.04-1.85(m,5H)。手性SFC A(45%MeOH):ee 100%,Rt=4.59min。

[1171] 2-苯基-2-((R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)噁唑-2-基)吡咯烷-1-基)乙酸(非对映异构化合物141-E1和141-E2)

[1172]

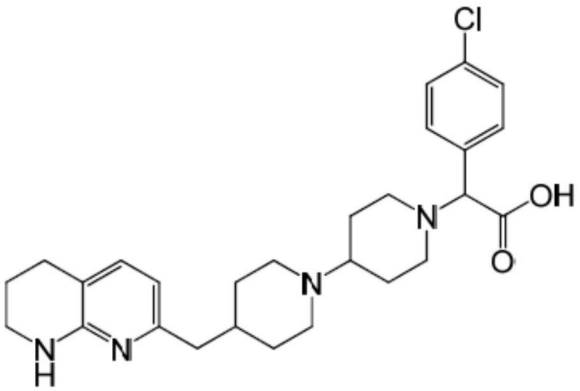


[1173] 化合物141-E1 LC/MS ESI 433(M+H)+^{1}H NMR(400MHz,MeOD)δ7.60-7.57(m,2H),7.49(s,1H),7.40-7.37(m,3H),7.11(d,J=7.6Hz,1H),6.34(d,J=7.2Hz,1H),4.34(s,1H),3.69-3.67(m,1H),3.50-3.23(m,5H),3.03-3.00(m,1H),2.82-2.80(m,4H),2.71-2.68(m,2H),2.39-2.37(m,1H),2.28-2.25(m,1H),1.89-1.86(m,2H)。

[1174] 化合物141-E2 LC/MS ESI 433(M+H)+^{1}H NMR(400MHz,MeOD)δ7.60-7.57(m,2H),7.51-7.50(m,1H),7.43-7.38(m,3H),7.16(d,J=7.2Hz,1H),6.37(d,J=7.2Hz,1H),4.45(s,1H),3.78-3.75(m,2H),3.39-3.23(m,7H),3.03-3.00(m,1H),2.85-2.83(m,4H),2.71-2.68(m,2H),2.39-2.37(m,1H),2.28-2.25(m,1H),1.89-1.83(m,2H)。

[1175] 2-(4-氯苯基)-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-基)乙酸(化合物142)

[1176]

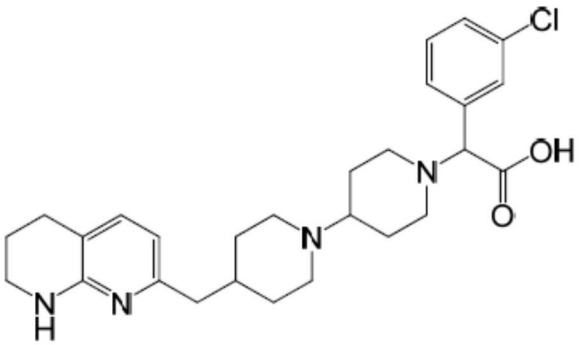


[1177] 化合物142 LC/MS ESI 483(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.50(d,J=8.8,2H),7.32(d,J=8.4,2H),7.14(d,J=7.2Hz,1H),6.35(d,J=7.2Hz,1H),3.80(s,1H),3.49-3.31(m,5H),2.95-2.69(m,6H),2.47(d,J=9.2Hz,2H),2.37-1.67(m,11H),1.51-1.38(m,2H)。

[1178] 2-(3-氯苯基)-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-

基)乙酸(化合物143)

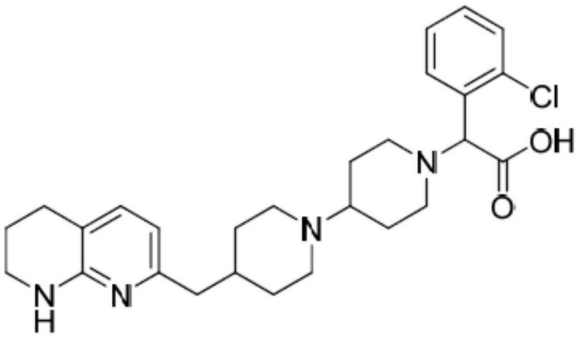
[1179]



[1180] 化合物143 LC/MS ESI 483.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.61(s,1H),7.44-7.42(m,1H),7.32-7.29(m,2H),7.16(d,J=7.0Hz,1H),6.38(d,J=7.3Hz,1H),3.86(s,1H),3.46-3.37(m,6H),3.01(m,1H),2.85(m,2H),2.79(t,J=6.2Hz,2H),2.51(t,J=7.5Hz,2H),2.25(s,2H),2.04(m.1H),1.97-1.84(m,8H),1.77(m,1H),1.65(m,2H)。

[1181] 2-(2-氯苯基)-2-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)-1,4'-联哌啶-1'-基)乙酸(对映异构化合物144-E1和144-E2)

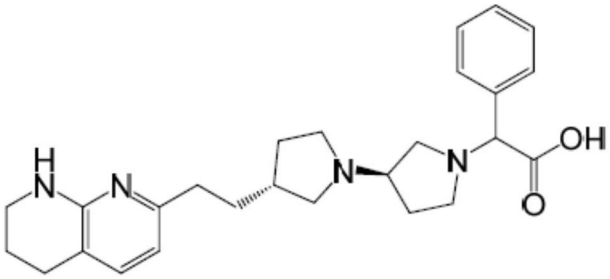
[1182]



[1183] 化合物144-E1 LC/MS ESI 483(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.82(dd,J=7.7,1.8Hz,1H),7.41(dd,J=7.8,1.3Hz,1H),7.32-7.15(m,2H),7.16(d,J=7.3Hz,1H),6.37(d,J=7.3Hz,1H),4.52(s,1H),3.48(d,J=10.5Hz,1H),3.43-3.35(m,4H),2.99(s,1H),2.88-2.74(m,3H),2.72(t,J=6.2Hz,2H),2.49(d,J=6.9Hz,2H),2.37(s,1H),2.22(s,1H),2.04(d,J=12.0Hz,1H),1.93-1.85(m,7H),1.77-1.67(m,1H),1.51-1.38(m,2H)。手性SFC I(50%EtOH):ee100%,Rt=8.05min。

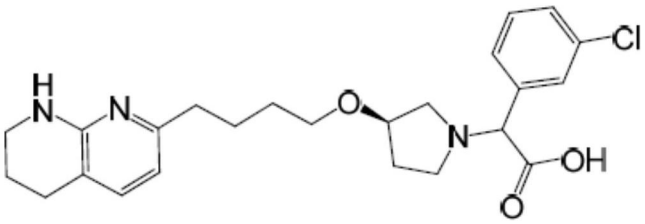
[1184] 化合物144-E2 LC/MS ESI 483(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.82(dd,J=7.6,1.8Hz,1H),7.41(dd,J=7.8,1.2Hz,1H),7.32-7.15(m,2H),7.16(d,J=7.3Hz,1H),6.37(d,J=7.3Hz,1H),4.52(s,1H),3.47(d,J=9.3Hz,1H),3.42-3.35(m,4H),2.99(s,1H),2.87-2.74(m,3H),2.72(t,J=6.2Hz,2H),2.49(d,J=6.9Hz,2H),2.37(s,1H),2.22(s,1H),2.04(d,J=12.7Hz,1H),1.94-1.82(m,7H),1.76-1.68(m,1H),1.49-1.42(m,2H)。手性SFC I(50%EtOH):ee 100%,Rt=11.00min。

[1185] 2-苯基-2-((3R,3'R)-3-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)-1,3'-联吡咯烷-1'-基)乙酸(化合物145)

[1186] 

[1187] 化合物145 LC/MS ESI 435.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.45-7.40(m,2H),7.25-7.18(m,3H),7.03-7.01(m,1H),6.27(t,J=7.5Hz,1H),3.78-3.74(m,1H),3.30-3.25(m,2H),3.15-2.90(m,2H),2.85-1.85(m,16H),1.80-1.44(m,6H)。

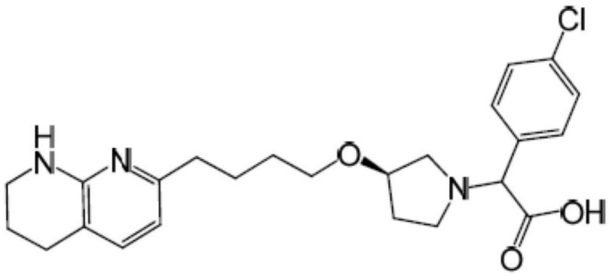
[1188] 2-(3-氯苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物146-E1和146-E2)

[1189] 

[1190] 化合物146-E1 LC/MS ESI 375.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.61(s,1H),7.48-7.39(m,3H),7.20(d,J=9.0Hz,1H),6.41(d,J=9.0Hz,1H),4.42(s,1H),4.16(s,1H),3.47-3.37(m,5H),3.13(m,1H),2.98(m,1H),2.73(t,J=8.0Hz,2H),2.58(t,J=9.5Hz,2H),2.09(s,2H),1.90-1.88(m,2H),1.74-1.59(m,5H)。手性SFC A(35%MeOH):ee 100%,Rt=2.81min。

[1191] 化合物146-E2 LC/MS ESI 375.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.62(s,1H),7.48-7.39(m,3H),7.20(d,J=9.0Hz,1H),6.41(d,J=9.0Hz,1H),4.33(s,1H),4.15(s,1H),3.47-3.37(m,4H),3.27(m,2H),3.05(m,2H),2.73(t,J=8.0Hz,2H),2.58(m,2H),2.09(s,1H),1.90-1.88(m,2H),1.74(m,2H),1.61(m,2H)。手性SFC A(35%MeOH):ee 100%,Rt=5.23min。

[1192] 2-(4-氯苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物147-E1和147-E2)

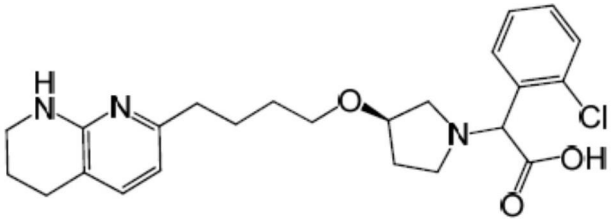
[1193] 

[1194] 化合物147-E1 LC/MS ESI 444(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.51(d,J=8.8,2H),7.42(d,J=8.8,2H),7.19(d,J=7.6Hz,1H),6.40(d,J=7.6Hz,1H),4.49-4.47(m,1H),4.17(s,1H),3.49-3.31(m,5H),3.25-2.91(m,3H),2.98(t,J=5.6Hz,2H),2.56(t,J=8.0Hz,2H),2.11-1.61(m,8H)。手性SFC A(40%MeOH):ee 100%,Rt=2.21min。

[1195] 化合物147-E2 LC/MS ESI 444(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.51(d,J=8.8,

2H),7.42(d,J=8.8,2H),7.19(d,J=7.6Hz,1H),6.40(d,J=7.6Hz,1H),4.41-4.37(m,1H),4.18(s,1H),3.49-3.31(m,4H),3.25-2.95(m,4H),2.71(t,J=6.4Hz,2H),2.65-2.56(m,2H),2.15-1.55(m,8H)。手性SFC A(40%MeOH):ee 100%,Rt=4.29min。

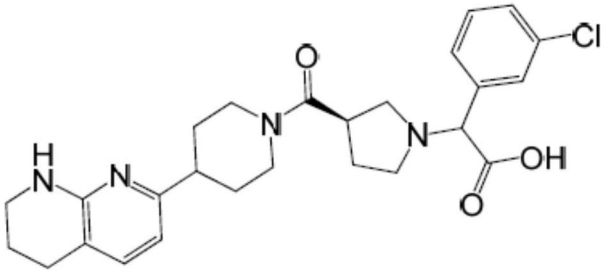
[1196] 2-(2-氯苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物148-E1和148-E2)

[1197] 

[1198] 化合物148-E1 LC/MS ESI 444(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.81-7.39(m,4H),7.19(d,J=7.2Hz,1H),6.40(d,J=7.6Hz,1H),5.03(s,1H),4.16(s,1H),3.49-3.31(m,5H),3.22-3.05(m,3H),2.73-2.55(m,4H),2.25-1.55(m,8H)。手性SFC F(45%MeOH):ee 100%,Rt=5.41min。

[1199] 化合物148-E2 LC/MS ESI 444(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.81-7.39(m,4H),7.19(d,J=7.2Hz,1H),6.40(d,J=7.6Hz,1H),5.16(s,1H),4.18(s,1H),3.49-3.31(m,5H),3.22-3.05(m,3H),2.73-2.55(m,4H),2.25-1.55(m,8H)。手性SFC F(45%MeOH):ee 100%,Rt=7.48min。

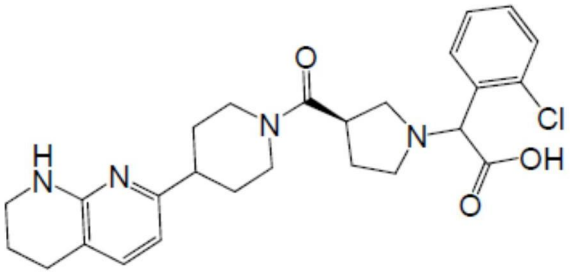
[1200] 2-(3-氯苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)吡咯烷-1-基)乙酸(非对映异构化合物149-E1和149-E2)

[1201] 

[1202] 化合物149-E1 LC/MS ESI 483.2(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.56(s,1H),7.52-7.41(m,3H),7.17-7.14(m,1H),6.38(d,J=7.2Hz,1H),4.63(d,J=11.6Hz,1H),4.53(s,1H),4.08(d,J=12.8Hz,1H),3.71-3.58(m,2H),3.40-2.98(m,6H),2.80-2.68(m,4H),2.38-1.85(m,6H),1.73-1.55(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=1.89min。

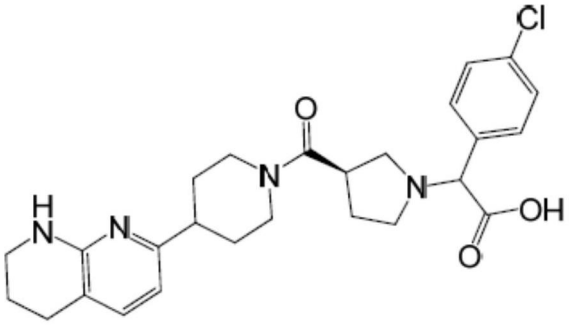
[1203] 化合物149-E2 LC/MS ESI 483.2(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.56(s,1H),7.52-7.41(m,3H),7.05(d,J=7.6Hz,1H),6.26(t,J=7.2Hz,1H),4.53(d,J=12.4Hz,1H),4.36(s,1H),3.95(d,J=14.0Hz,1H),3.51-3.38(m,5H),3.18-2.84(m,3H),2.68-2.55(m,4H),2.31-1.75(m,6H),1.60-1.45(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=3.40min。

[1204] 2-(2-氯苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)吡咯烷-1-基)乙酸(化合物150)

[1205] 

[1206] 化合物150LC/MS ESI 483.2(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.81-7.75(m,1H),7.58-7.38(m,3H),7.16(d,J=7.2Hz,1H),6.40-6.35(m,1H),5.24-5.10(m,1H),4.65-4.61(m,1H),4.10-4.06(m,1H),3.71-2.98(m,8H),2.80-2.68(m,4H),2.38-1.81(m,6H),1.75-1.55(m,2H)。

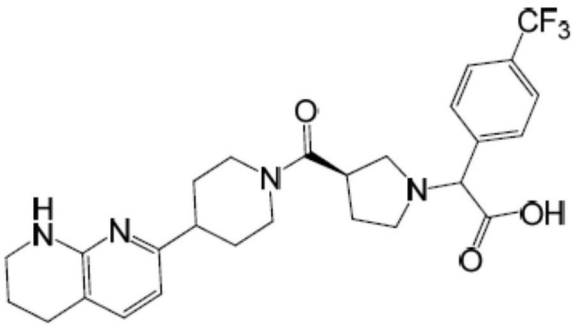
[1207] 2-(4-氯苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)吡咯烷-1-基)乙酸(非对映异构化合物151-E1和151-E2)

[1208] 

[1209] 化合物151-E1 LC/MS ESI 483.2(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.58(d,J=7.4Hz,2H),7.45(d,J=7.4Hz,2H),7.19-7.14(m,1H),6.39-6.36(m,1H),4.65-4.60(m,2H),4.08(d,J=12.4Hz,1H),3.75-3.58(m,2H),3.40-2.91(m,6H),2.79-2.65(m,4H),2.38-1.82(m,6H),1.72-1.55(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=1.96min。

[1210] 化合物151-E2 LC/MS ESI 483.2(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.48-7.45(m,2H),7.33(d,J=8.4Hz,2H),7.04(d,J=7.2Hz,1H),6.26(t,J=7.2Hz,1H),4.50(d,J=13.2Hz,1H),4.39(s,1H),3.95(d,J=13.2Hz,1H),3.55-3.31(m,5H),3.18-2.85(m,3H),2.70-2.55(m,4H),2.31-1.72(m,6H),1.60-1.41(m,2H)。手性SFC A(45%MeOH):ee 100%,Rt=3.71min。

[1211] 2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)哌啶-1-羰基)吡咯烷-1-基)-2-(4-(三氟甲基)苯基)乙酸(非对映异构化合物152-E1和152-E2)

[1212] 

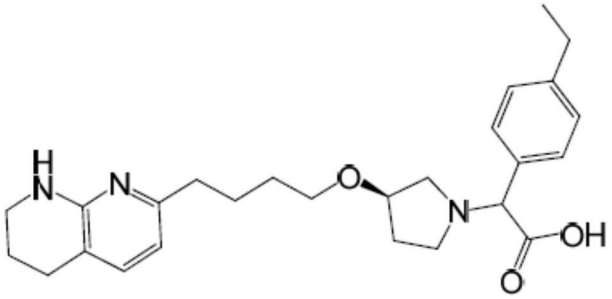
[1213] 化合物152-E1 LC/MS ESI 517(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.80-7.74(m,4H),

7.18(t,J=6.4Hz,1H),6.39(d,J=7.2Hz,1H),4.71-4.63(m,2H),4.08(d,J=13.2Hz,1H),3.76-3.58(m,2H),3.42-2.91(m,6H),2.79-2.65(m,4H),2.38-1.82(m,6H),1.72-1.55(m,2H)。手性SFC A(35%MeOH):ee 100%,Rt=2.47min。

[1214] 化合物152-E2 LC/MS ESI 517$(M+H)^+$。^{1}H NMR(400MHz,MeOD)δ7.68-7.56(m,4H),7.03(d,J=6.8Hz,1H),6.28-6.23(m,1H),4.52(d,J=12.8Hz,1H),4.23-4.19(m,1H),3.99-3.96(m,1H),3.45-2.65(m,8H),2.62-2.55(m,4H),2.21-1.72(m,6H),1.59-1.42(m,2H)。手性SFC A(35%MeOH):ee 100%,Rt=3.81min。

[1215] 2-(4-乙基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物153-E1和153-E2)

[1216]

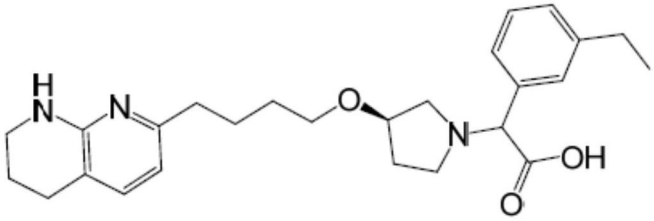


[1217] 化合物153-E1 LC/MS ESI 438$(M+H)^+$^{1}H NMR(400MHz,MeOD)δ7.43(d,J=8.4,2H),7.26(d,J=8.0,2H),7.15(d,J=7.2Hz,1H),6.38(d,J=7.2Hz,1H),4.46(s,1H),4.18(s,1H),3.55-2.95(m,8H),2.73-2.53(m,6H),2.18-1.56(m,8H),1.23(t,J=7.6Hz,3H)。手性SFC A(35%MeOH):ee 100%,Rt=2.86min。

[1218] 化合物153-E2 LC/MS ESI 438$(M+H)^+$^{1}H NMR(400MHz,MeOD)δ7.43(d,J=8.4,2H),7.26(d,J=8.0,2H),7.15(d,J=7.2Hz,1H),6.38(d,J=7.2Hz,1H),4.34(s,1H),4.05(s,1H),3.41-2.95(m,8H),2.61-2.38(m,6H),2.10-1.46(m,8H),1.13(t,J=7.6Hz,3H)。手性SFC A(35%MeOH):ee 100%,Rt=4.99min。

[1219] 2-(3-乙基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物154-E1和154-E2)

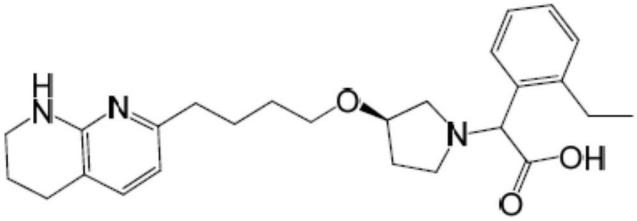
[1220]



[1221] 化合物154-E1 LC/MS ESI 438$(M+H)^+$^{1}H NMR(400MHz,MeOD)δ7.40-7.25(m,4H),7.14(d,J=7.2Hz,1H),6.38(d,J=7.2Hz,1H),4.45(s,1H),4.18(s,1H),3.53-2.95(m,8H),2.72-2.52(m,6H),2.15-1.56(m,8H),1.35(t,3H)。手性SFC A(40%MeOH):ee 100%,Rt=1.88min。

[1222] 化合物154-E2 LC/MS ESI 438$(M+H)^+$^{1}H NMR(400MHz,MeOD)δ7.30-7.14(m,4H),7.04(d,J=7.2Hz,1H),6.28(d,J=7.2Hz,1H),4.34(s,1H),4.06(s,1H),3.43-2.99(m,8H),2.62-2.42(m,6H),2.15-1.46(m,8H),1.25(t,3H)。手性SFC A(40%MeOH):ee 100%,Rt=3.59min。

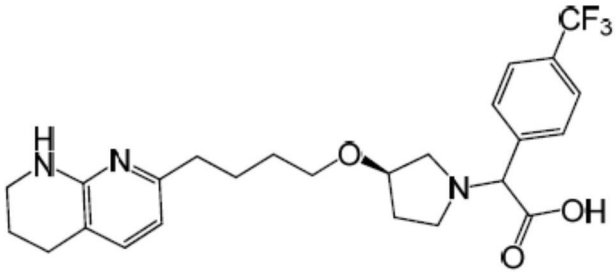
[1223] 2-(2-乙基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物155-E1和155-E2)

[1224] 

[1225] 化合物155-E1 LC/MS ESI 438(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.62(d,J=7.6,1H),7.32-7.14(m,4H),6.38(d,J=7.2Hz,1H),4.83(s,1H),4.15(s,1H),3.53-3.15(m,8H),2.91-2.53(m,6H),2.18-1.56(m,8H),1.35(t,3H)。手性SFC F(30%MeOH):ee 100%,Rt=3.28min。

[1226] 化合物155-E2 LC/MS ESI 438(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.62(d,J=7.6,1H),7.32-7.14(m,4H),6.38(d,J=7.2Hz,1H),4.73(s,1H),4.15(s,1H),3.53-3.15(m,8H),2.91-2.53(m,6H),2.18-1.56(m,8H),1.35(t,3H)。手性SFC F(30%MeOH):ee 100%,Rt=6.54min。

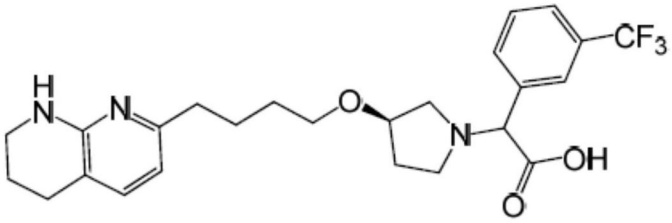
[1227] 2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-(4-(三氟甲基)苯基)乙酸(非对映异构化合物156-E1和156-E2)

[1228] 

[1229] 化合物156-E1 LC/MS ESI 478(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.75-7.70(m,4H),7.20(d,J=7.2Hz,1H),6.41(d,J=7.2Hz,1H),4.42(s,1H),4.15(s,1H),3.51-2.95(m,8H),2.74-2.53(m,4H),2.18-1.56(m,8H)。手性SFC A(35%MeOH):ee 100%,Rt=1.73min。

[1230] 化合物156-E2 LC/MS ESI 478(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.75-7.70(m,4H),7.22(d,J=7.6Hz,1H),6.42(d,J=7.2Hz,1H),4.53(s,1H),4.16(s,1H),3.51-2.95(m,8H),2.74-2.53(m,4H),2.18-1.56(m,8H)。手性SFC A(35%MeOH):ee 100%,Rt=2.72min。

[1231] 2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-(3-(三氟甲基)苯基)乙酸(非对映异构化合物157-E1和157-E2)

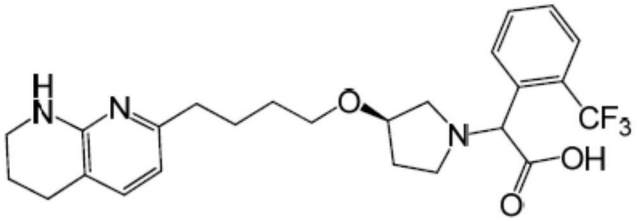
[1232] 

[1233] 化合物157-E1 LC/MS ESI 478(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.91(s,1H),7.80(d,J=7.6Hz,1H),7.61-7.50(m,2H),7.15(d,J=7.6Hz,1H),6.37(d,J=7.6Hz,1H),4.10-4.04(m,2H),3.49-2.85(m,5H),2.75-2.51(m,7H),2.18-1.56(m,8H)。手性SFC A(25%

MeOH):ee 100%,Rt=3.28min。

[1234] 化合物157-E2 LC/MS ESI 478(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.93(s,1H),7.80(d,J=7.6Hz,1H),7.61-7.50(m,2H),7.21(d,J=7.2Hz,1H),6.41(d,J=7.6Hz,1H),4.38(s,1H),4.15(s,1H),3.50-2.95(m,8H),2.73-2.51(m,4H),2.18-1.56(m,8H)。手性SFC A(25% MeOH):ee 100%,Rt=4.83min。

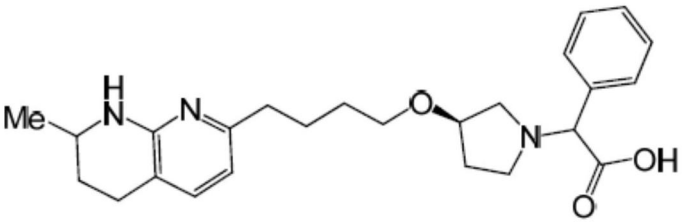
[1235] 2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-(2-(三氟甲基)苯基)乙酸(非对映异构化合物158-E1和158-E2)

[1236] 

[1237] 化合物158-E1 LC/MS ESI 478(M+H)$^{+1}$H NMR(400MHz,MeOD)δ8.01(d,J=8.0Hz,1H),7.76(d,J=7.6Hz,1H),7.67(t,J=7.2Hz,1H),7.54(t,J=7.6Hz,1H),7.19(d,J=7.2Hz,1H),6.40(d,J=7.2Hz,1H),4.62(s,1H),4.13(s,1H),3.49-2.85(m,8H),2.73-2.55(m,4H),2.16-1.56(m,8H)。

[1238] 化合物158-E2 LC/MS ESI 478(M+H)$^{+1}$H NMR(400MHz,MeOD)δ8.01(d,J=8.0Hz,1H),7.76(d,J=7.6Hz,1H),7.67(t,J=7.2Hz,1H),7.54(t,J=7.6Hz,1H),7.19(d,J=7.2Hz,1H),6.40(d,J=7.2Hz,1H),4.73(s,1H),4.13(s,1H),3.49-2.85(m,8H),2.73-2.55(m,4H),2.16-1.56(m,8H)。

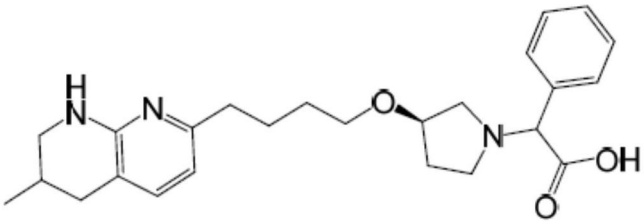
[1239] 2-((3R)-3-(4-(7-甲基-5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-苯基乙酸(非对映异构化合物159-E1和159-E2)

[1240] 

[1241] 化合物159-E1 LC/MS ESI 424(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.76-7.53(m,2H),7.42-7.40(m,3H),7.19(d,J=7.2Hz,1H),6.40(d,J=7.2Hz,1H),4.48(s,1H),4.18-4.16(m,1H),3.55-3.24(m,5H),3.16-2.98(m,2H),2.75-2.53(m,4H),2.16-1.45(m,8H),1.22(d,J=7.2Hz,3H)。手性SFC A(30%MeOH):ee 100%,Rt=2.50min。

[1242] 化合物159-E2 LC/MS ESI 424(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.76-7.53(m,2H),7.42-7.40(m,3H),7.19(d,J=7.2Hz,1H),6.40(d,J=7.2Hz,1H),4.39(s,1H),4.18-4.16(m,1H),3.65-3.20(m,5H),3.18-3.02(m,2H),2.75-2.53(m,4H),2.21-1.45(m,8H),1.22(d,J=7.2Hz,3H)。手性SFC A(30%MeOH):ee 100%,Rt=4.40min。

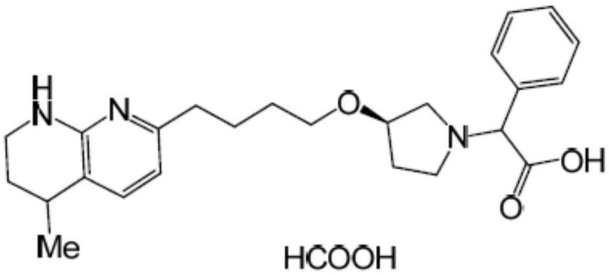
[1243] 2-((3R)-3-(4-(6-甲基-5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-苯基乙酸(非对映异构化合物160-E1和160-E2)

[1244] 

[1245] 化合物160-E1 LC/MS ESI 424(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.55-7.53(m,2H),7.42-7.40(m,3H),7.16(d,J=7.2Hz,1H),6.38(d,J=7.2Hz,1H),4.46(s,1H),4.18-4.16(m,1H),3.58-3.24(m,5H),3.16-2.91(m,3H),2.78-2.35(m,4H),2.16-1.45(m,7H),1.04(d,J=6.4Hz,3H)。手性SFC A(40%MeOH):ee 100%,Rt=1.83min。

[1246] 化合物160-E2 LC/MS ESI 424(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.55-7.53(m,2H),7.42-7.40(m,3H),7.16(d,J=7.2Hz,1H),6.38(d,J=7.2Hz,1H),4.44(s,1H),4.18-4.16(m,1H),3.48-3.24(m,5H),3.16-2.91(m,3H),2.78-2.35(m,4H),2.16-1.90(m,4H),1.75-1.50(m,3H),1.04(d,J=6.4Hz,3H)。手性SFC A(40%MeOH):ee 100%,Rt=2.84min。

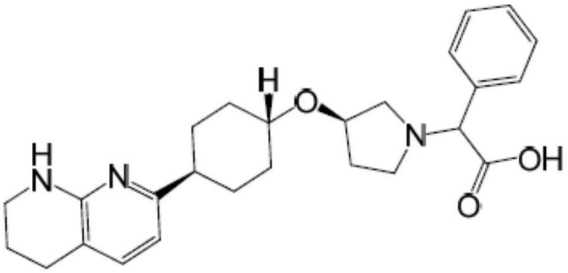
[1247] 2-((3R)-3-(4-(5-甲基-5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-苯基乙酸(非对映异构化合物161-E1和161-E2)

[1248] 

[1249] 化合物161-E1 LC/MS ESI 424(M+H)+^{1}H NMR(400MHz,MeOD)δ8.54(s,1H),7.58-7.57(m,3H),7.45-7.43(m,3H),6.57(d,J=7.6Hz,1H),4.62(s,1H),4.21-4.19(m,1H),3.51-3.40(m,6H),3.27-3.21(m,2H),2.95-2.91(m,1H),2.72-2.68(m,2H),2.16-2.14(m,2H),1.96-1.94(m,1H),1.71-1.63(m,5H),1.30(d,J=6.8Hz,1H)。

[1250] 化合物161-E2 LC/MS ESI 424(M+H)+^{1}H NMR(400MHz,MeOD)δ8.53(s,1H),7.57-7.55(m,3H),7.46-7.44(m,3H),6.56(d,J=7.2Hz,1H),4.67(s,1H),4.21-4.19(m,1H),3.51-3.40(m,5H),3.11-3.09(m,1H),2.93-2.91(m,1H),2.72-2.65(m,2H),2.16-2.14(m,1H),1.96-1.94(m,1H),1.71-1.63(m,5H),1.30(d,J=6.8Hz,1H)。

[1251] 2-苯基-2-((R)-3-((1r,4R)-4-(5,6,7,8-四氢-1,8-萘啶-2-基)环己基氧基)吡咯烷-1-基)乙酸(非对映异构化合物162-E1和162-E2)

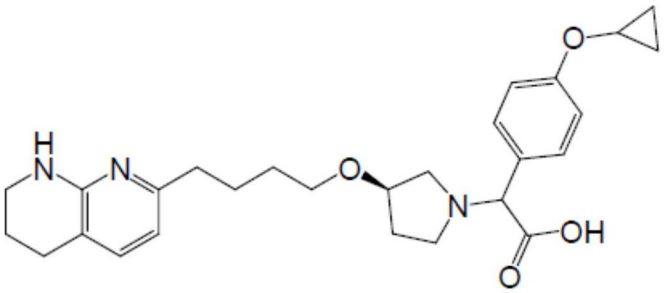
[1252] 

[1253] 化合物162-E1 LC/MS ESI 436.2(M+H)+。^{1}H NMR(500MHz,CD3OD)δ7.59-7.58(m,2H),7.45-7.44(m,3H),7.14(d,J=7.5Hz,1H),6.37(d,J=7.5Hz,1H),4.46-4.42(m,2H),

3.40-3.33(m,4H),3.19-3.17(m,2H),2.72-2.69(m,2H),2.42-2.38(m,1H),2.26-2.22(m,1H),2.14-2.12(m,3H),1.94-1.86(m,4H),1.54-1.52(m,2H)1.43-1.30(m,3H)。手性SFC B(40%MeOH):ee 100%,Rt=1.83min。

[1254] 化合物162-E2 LC/MS ESI 436.2(M+H)+。^{1}H NMR(500MHz,CD3OD)δ7.59-7.57(m,2H),7.47-7.44(m,3H),7.14(d,J=8.0Hz,1H),6.38(d,J=8.0Hz,1H),4.47-4.44(m,2H),3.61-3.59(m,1H),3.36-3.33(m,3H),3.06-2.99(m,2H),2.72-2.69(m,2H),2.43-2.38(m,1H),2.18-2.07(m,4H),1.94-1.86(m,4H),1.46-1.38(m,2H)1.31-1.16(m,3H)。手性SFC B(40%MeOH):ee 95.0%,Rt=3.14min。

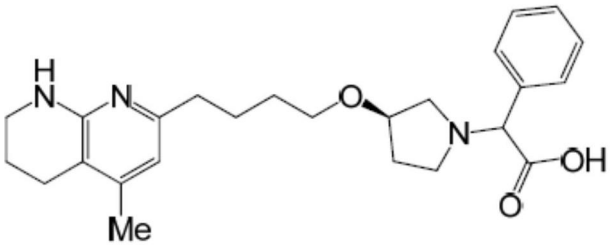
[1255] 2-(4-环丙氧基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物163-E1和163-E2)

[1256] 

[1257] 化合物163-E1 LC/MS ESI 466.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.47-7.45(m,2H),7.16-7.07(m,3H),6.383(d,J=7.6Hz,1H),4.456(s,1H),4.19(s,1H),3.82-3.78(m,1H),3.46-3.31(m,6H),3.21-3.15(m,2H),2.70-2.68(m,2H),2.55-2.53(m,2H),2.22-2.16(m,2H),1.95-1.91(m,2H),1.88-1.55(m,4H),0.81-0.79(m,2H),0.69-0.68(m,2H)。

[1258] 化合物163-E2 LC/MS ESI 466.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.462-7.44(m,2H),7.16-7.08(m,3H),6.387(d,J=7.2Hz,1H),4.462(s,1H),4.19(s,1H),3.82-3.78(m,1H),3.46-3.31(m,6H),3.21-3.15(m,2H),2.72-2.69(m,2H),2.56-2.53(m,2H),2.2-2.00(m,2H),1.89-1.86(m,2H),1.78-1.60(m,4H),0.81-0.79(m,2H),0.69-0.68(m,2H)。

[1259] 2-((R)-3-(4-(4-甲基-5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-苯基乙酸(非对映异构化合物164-E1和164-E2)

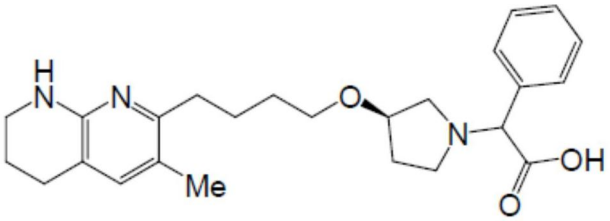
[1260] 

[1261] 化合物164-E1 LC/MS ESI 424.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.54-7.41(m,5H),6.37(s,1H),4.45(s,1H),4.17(s,1H),3.45-2.91(m,8H),2.68-2.52(m 4H),2.17(s,3H),2.15-1.55(m,8H)。手性SFC B(30%MeOH):ee100%,Rt=1.48min。

[1262] 化合物164-E2 LC/MS ESI 424.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.55-7.41(m,5H),6.37(s,1H),4.41(s,1H),4.16(s,1H),3.45-3.05(m,8H),2.68-2.52(m 4H),2.17(s,3H),2.15-1.55(m,8H)。手性SFC B(30%MeOH):ee100%,Rt=2.66min。

[1263] 2-((R)-3-(4-(3-甲基-5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)-2-

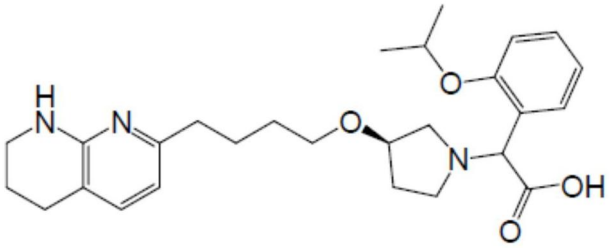
苯基乙酸(非对映异构化合物165-E1和165-E2)

[1264] 

[1265] 化合物165-E1 LC/MS ESI 424.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.54(s,2H),7.41(m,3H),7.08(s,1H),4.44(s,1H),4.16(s,1H),3.45(m,3H),3.21(m,2H),3.18(m,2H),2.98(m,1H),2.77-2.58(m 4H),2.09(s,5H),1.88(m,2H),1.67(m,4H)。手性SFC A(40%MeOH):ee 100%,Rt=2.36min。

[1266] 化合物165-E2 LC/MS ESI 424.1(M+H)$^+$。^{1}H NMR(500MHz,MeODδ7.54(s,2H),7.41(m,3H),7.06(s,1H),4.40(s,1H),4.19(s,1H),3.45(m,6H),3.18(m,2H),2.77-2.58(m 4H),2.09(m,5H),1.88(m,2H),1.67(m,4H)。手性SFC A(40%MeOH):ee 99%,Rt=3.55min。

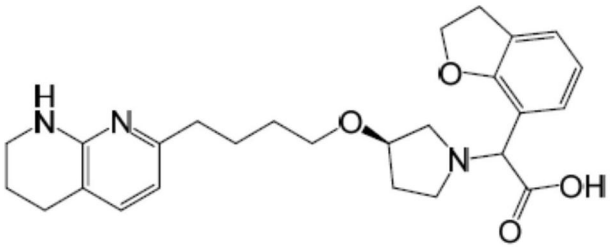
[1267] 2-(2-异丙氧基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物166-P1和166-P2)

[1268] 

[1269] 化合物166-P1 LC/MS ESI 468.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.55(d,J=6.4Hz,1H),7.38-7.35(m,1H),7.15-6.95(m,3H),6.37(d,J=7.6Hz,1H),4.99(s,1H),4.89-4.72(m,1H),4.19(s,1H),3.64-3.36(m,6H),3.24-3.20(m,2H),2.72-2.68(m,2H),2.55-2.51(m,2H),2.14-2.11(m,2H),1.89-1.86(m,2H),1.71-1.56(m,4H),1.38-1.35(m,6H)。

[1270] 化合物166-P2 LC/MS ESI 468.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.51(d,J=6.8Hz,1H),7.38-7.35(m,1H),7.15-6.95(m,3H),6.37(d,J=6.8Hz,1H),5.06(s,1H),4.74--4.71(m,1H),4.18(s,1H),3.64-3.36(m,6H),3.24-3.05(m,2H),2.72-2.68(m,2H),2.55-2.51(m,2H),2.20-2.00(m,2H),1.89-1.86(m,2H),1.71-1.56(m,4H),1.38-1.35(m,6H)。

[1271] 2-(2,3-二氢苯并呋喃-7-基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物167-P1和167-P2)

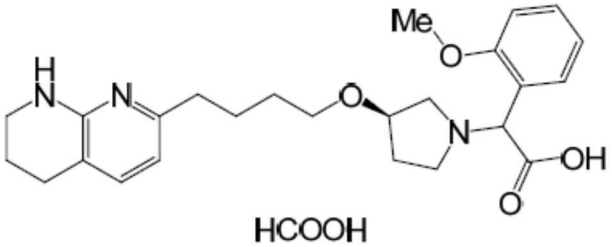
[1272] 

[1273] 化合物167-P1 LC/MS ESI 452(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.26(d,J=7.6Hz,

2H),7.15(d,J=7.2Hz,1H),6.88(t,J=7.6Hz,1H),6.38(d,J=7.2Hz,1H),4.83(s,1H),4.56(t,J=7.6Hz,2H),4.15(s,1H),3.55-3.15(m,10H),2.71-2.52(m,4H),2.20-1.56(m,8H)。手性SFC C(25%MeOH):ee 100%,Rt=0.97min。

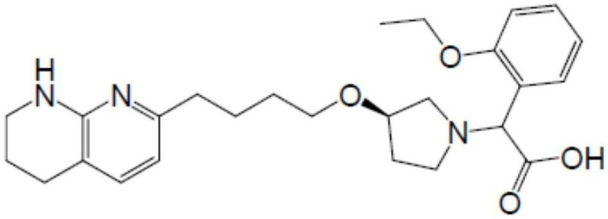
[1274] 化合物167-P2 LC/MS ESI 452(M+H)$^{+1}$H NMR(400MHz,MeOD)δ7.30-7.25(m,2H),7.15(d,J=7.2Hz,1H),6.88(t,J=7.6Hz,1H),6.38(d,J=7.2Hz,1H),4.78(s,1H),4.60(t,J=8.4Hz,2H),4.15(s,1H),3.55-3.15(m,10H),2.71-2.52(m,4H),2.20-1.56(m,8H)。手性SFC C(25%MeOH):ee 100%,Rt=1.73min。

[1275] 2-(2-甲氧基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(化合物168)

[1276] 

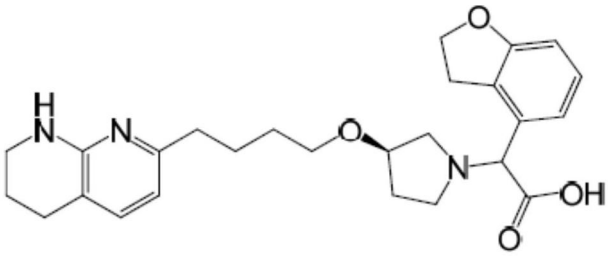
[1277] 化合物168 LC/MS ESI 440(M+H)+^{1}H NMR(400MHz,MeOD)δ8.38(s,1H),7.41-7.33(m,3H),7.02-6.92(m,2H),6.48-6.44(m,1H),4.94-4.79(m,1H),4.20-4.15(m,1H),3.77-2.95(m,11H),2.58-2.50(m,4H),2.15-1.49(m,8H)。

[1278] 2-(2-乙氧基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(化合物169)

[1279] 

[1280] 化合物169 LC/MS ESI 454(M+H)+^{1}H NMR(400MHz,MeOD)δ7.52(t,J=4.8Hz,1H),7.41(t,J=4.8Hz,1H),7.15-6.98(m,3H),6.39-6.35(m,1H),5.09-5.02(m,1H),4.17-4.10(m,3H),3.55-3.11(m,8H),2.72-2.50(m,4H),2.15-1.38(m,11H)。

[1281] 2-(2,3-二氢苯并呋喃-4-基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物170-E1和170-E2)

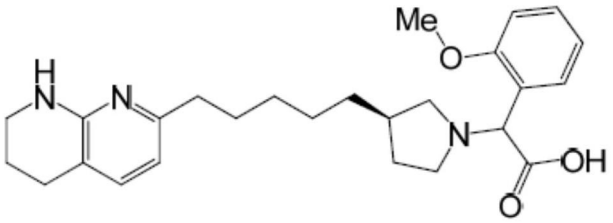
[1282] 

[1283] 化合物170-E1 LC/MS ESI 452.2(M+H)+。^{1}H NMR(500MHz,CD_3OD)δ7.18-7.15(m,2H),7.08-7.04(m,1H),6.77(d,J=8.0Hz,1H),6.41-6.38(m,1H),4.59-4.52(m,3H),4.21-4.19(m,1H),3.54-3.38(m,6H),3.29-3.20(m,3H),3.11-3.07(m,1H),2.72(t,J=6.0Hz,2H),2.56(t,J=7.0Hz,2H),2.17-2.07(m,2H),1.92-1.88(m,2H),1.76-1.71(m,2H),1.70-

1.59(m,2H)。手性SFC A(40%MeOH):ee 41.7%,Rt=2.55min。

[1284] 化合物170-E2 LC/MS ESI 452.2(M+H)+。^{1}H NMR(500MHz,CD3OD)δ7.18-7.15(m,2H),7.08-7.04(m,1H),6.77(d,J=8.0Hz,1H),6.41-6.39(m,1H),4.59-4.52(m,3H),4.20-4.18(m,1H),3.54-3.36(m,6H),3.30-3.09(m,4H),2.72(t,J=6.5Hz,2H),2.60-2.53(m,2H),2.20-2.18(m,2H),1.91-1.87(m,2H),1.76-1.65(m,2H),1.63-1.59(m,2H)。手性SFC A(40%MeOH):ee 57.7%,Rt=4.22min。

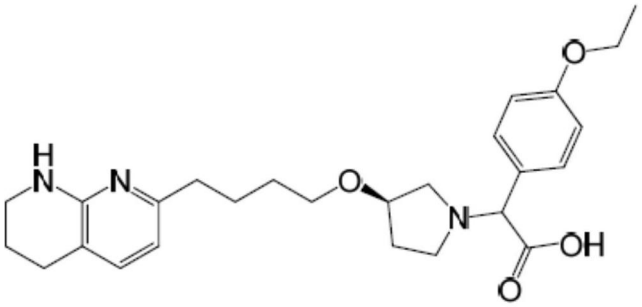
[1285] 2-(2-甲氧基苯基)-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)吡咯烷-1-基)乙酸(非对映异构化合物171-E1和171-E2)

[1286] 

[1287] 化合物171-E1 LC/MS ESI 438.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.50-7.43(m,3H),7.12-7.03(m,2H),6.52(d,J=7.6Hz,1H),5.01(s,1H),3.91(s,3H),3.47-3.43(m,3H),3.33-3.00(m,3H),2.80-2.77(m,2H),2.65-2.62(m,2H),2.40-2.10(m,2H),1.95-1.85(m,2H),1.75-1.68(m,3H),1.52-1.24(m,6H).

[1288] 化合物171-E2 LC/MS ESI 438.3(M+H)$^+$。^{1}H NMR(400MHz,MeOD)δ7.55-7.43(m,3H),7.12-7.03(m,2H),6.52(d,J=7.2Hz,1H),5.04(s,1H),3.91(s,3H),3.47-3.43(m,4H),3.21-3.11(m,1H),2.80-2.63(m,5H),2.45-2.12(m,2H),1.94-1.91(m,2H),1.68-1.65(m,3H),1.52-1.24(m,6H)。

[1289] 2-(4-乙氧基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物172-E1和172-E2)

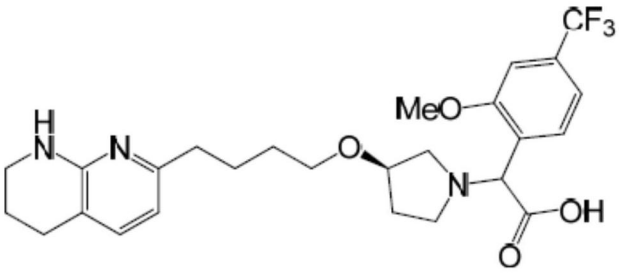
[1290] 

[1291] 化合物172-E1 LC/MS ESI 454(M+H)+^{1}H NMR(400MHz,MeOD)δ7.46(d,J=8.4Hz,2H),7.17(d,J=7.2Hz,1H),6.93(d,J=8.4Hz,2H),6.37(d,J=7.2Hz,1H),4.42(s,1H),4.16(s,1H),4.04(q,J=6.8Hz,2H),3.50-3.11(m,8H),2.72-2.52(m,4H),2.20-1.55(m,8H),1.38(t,J=6.8Hz,3H)。手性SFC B(30%MeOH):ee 100%,Rt=1.59min。

[1292] 化合物172-E2 LC/MS ESI 454(M+H)+^{1}H NMR(400MHz,MeOD)δ7.46(d,J=8.4Hz,2H),7.17(d,J=7.2Hz,1H),6.93(d,J=8.4Hz,2H),6.37(d,J=7.2Hz,1H),4.39(s,1H),4.17(s,1H),4.04(q,J=6.8Hz,2H),3.50-2.95(m,8H),2.70(t,J=6.0Hz,2H),2.54(t,J=7.2Hz,2H),2.10-1.45(m,8H),1.38(t,J=6.8Hz,3H)。手性SFC B(30%MeOH):ee 100%,Rt=4.18min。

[1293] 2-(2-甲氧基-4-(三氟甲基)苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物173-E1和173-E2)

[1294]

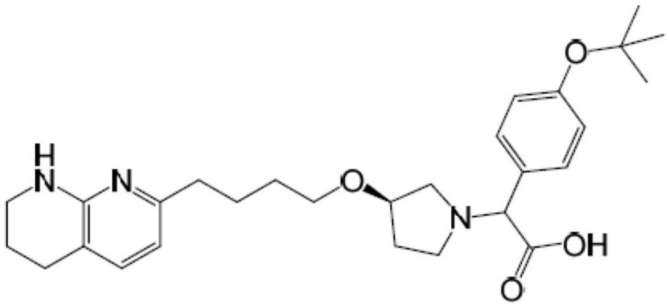


[1295] 化合物173-E1 LC/MS ESI 508(M+H)+ ^{1}H NMR(400MHz,MeOD)δ7.67(d,J=7.9Hz,1H),7.32(d,J=10.7Hz,2H),7.17(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),5.05(s,1H),4.19(s,1H),3.95(s,3H),3.70-3.32(m,6H),3.12-3.08(m,2H),2.64-2.54(m,4H),2.13-1.49(m,8H)。手性SFC A(35%MeOH):ee100%,Rt=2.34min。

[1296] 化合物173-E2 LC/MS ESI 508(M+H)+ ^{1}H NMR(400MHz,MeOD)δ7.67(d,J=7.9Hz,1H),7.32(d,J=10.7Hz,2H),7.17(d,J=7.3Hz,1H),6.40(d,J=7.3Hz,1H),5.08(s,1H),4.21(s,1H),3.95(s,3H),3.70-3.32(m,6H),3.12-3.08(m,2H),2.64-2.54(m,4H),2.13-1.49(m,8H)。手性SFC A(35%MeOH):ee100%,Rt=3.25min。

[1297] 2-(4-叔丁氧基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(化合物174)

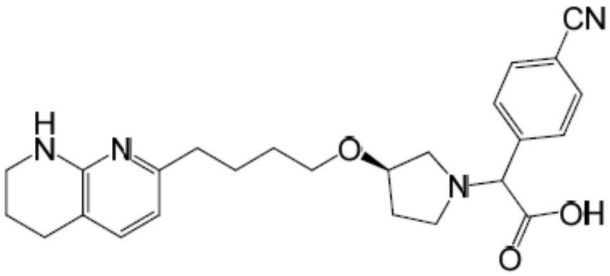
[1298]



[1299] 化合物174 LC/MS ESI 482(M+H)+ ^{1}H NMR(400MHz,MeOD)δ7.45(d,J=8.4Hz,2H),7.15(d,J=7.6Hz,1H),7.03(d,J=8.4Hz,2H),6.39(d,J=7.6Hz,1H),4.47(s,1H),4.19(s,1H),3.55-3.32(m,6H),3.20-3.05(m,2H),2.75-2.54(m,4H),2.20-1.58(m,8H),1.36(s,9H)。

[1300] 2-(4-氰基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物175-E1和175-E2)

[1301]

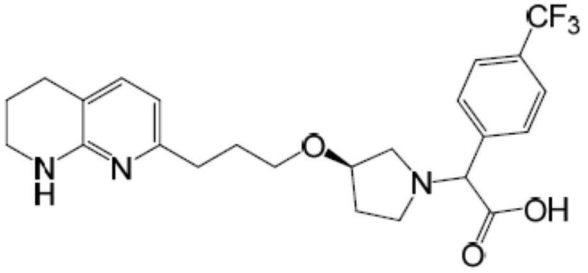


[1302] 化合物175-E1 LC/MS ESI 435(M+H)+ ^{1}H NMR(400MHz,MeOD)δ7.77-7.71(m,4H),7.26(d,J=7.6Hz,1H),6.44(d,J=7.6Hz,1H),4.31(s,1H),4.16-4.11(m,1H),3.51-3.29

(m,5H),3.20-2.97(m,3H),2.75-2.59(m,4H),2.22-1.65(m,8H)。手性SFC B(30%MeOH):ee 100%,Rt=1.26min。

[1303] 化合物175-E2 LC/MS ESI 435(M+H)+ ^{1}H NMR(400MHz,MeOD)δ7.77-7.71(m,4H),7.26(d,J=7.6Hz,1H),6.44(d,J=7.6Hz,1H),4.48(s,1H),4.16-4.11(m,1H),3.51-3.15(m,7H),2.85-2.57(m,5H),2.15-1.55(m,8H)。手性SFC B(30%MeOH):ee 100%,Rt=3.06min。

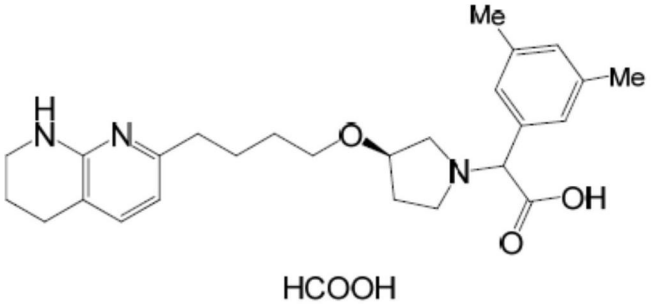
[1304] 2-((R)-3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙氧基)吡咯烷-1-基)-2-(4-(三氟甲基)苯基)乙酸(非对映异构化合物176-E1和176-E2)

[1305] 

[1306] 化合物176-E1 LC/MS ESI 464(M+H)+ ^{1}H NMR(400MHz,MeOD)δ7.76(d,J=8.4Hz,2H),7.69(d,J=8.0Hz,2H),7.17(d,J=7.2Hz,1H),6.39(d,J=7.2Hz,1H),4.30(s,1H),4.12(s,1H),3.44-3.37(m,4H),3.20-2.89(m,4H),2.72-2.59(m,4H),2.20-1.85(m,6H)。手性SFC B(35%MeOH):ee 100%,Rt=0.79min

[1307] 化合物176-E2 LC/MS ESI 464(M+H)+ ^{1}H NMR(400MHz,MeOD)δ7.76(d,J=8.4Hz,2H),7.69(d,J=8.0Hz,2H),7.17(d,J=7.2Hz,1H),6.39(d,J=7.2Hz,1H),4.20(s,1H),4.11(s,1H),3.44-3.28(m,5H),3.09-2.95(m,1H),2.78-2.55(m,6H),2.10-1.85(m,6H)。手性SFC B(35%MeOH):ee 90%,Rt=2.65min

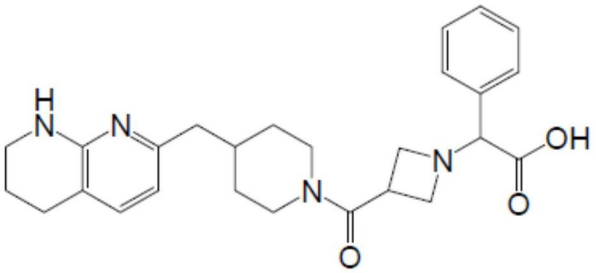
[1308] 2-(3,5-二甲基苯基)-2-((R)-3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)吡咯烷-1-基)乙酸(非对映异构化合物177-E1和177-E2)

[1309] 

[1310] 化合物177-E1 LC/MS ESI 438(M+H)+。^{1}H NMR(400MHz,MeOD)δ8.51(s,1H),7.49(d,J=7.6Hz,1H),7.18(s,2H),7.08(s,1H),6.55(d,J=7.2Hz,1H),4.55(s,1H),4.19(s,1H),3.52-3.24(m,9H),2.80-2.69(m,4H),2.31-2.15(m,8H),1.93-1.65(m,6H)。

[1311] 化合物177-E2 LC/MS ESI 438(M+H)+。^{1}H NMR(400MHz,MeOD)δ8.51(s,1H),7.49(d,J=7.6Hz,1H),7.18(s,2H),7.08(s,1H),6.55(d,J=7.2Hz,1H),4.59(s,1H),4.20(s,1H),3.50-3.10(m,9H),2.80-2.68(m,4H),2.31-2.15(m,8H),1.93-1.65(m,6H)。

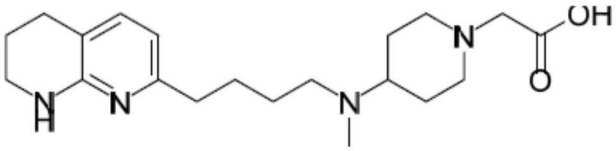
[1312] 2-苯基-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(对映异构化合物178-E1和178-E2)

[1313] 

[1314] 化合物178-E1 LC/MS ESI 449.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.51(d,J=7.6Hz,2H),7.41(d,J=6.5Hz,3H),7.15(d,J=7.1Hz,1H),6.35(d,J=7.3Hz,1H),4.47(d,J=13.4Hz,2H),4.19(s,1H),3.86(M,4H),3.64-3.54(m,1H),3.43-3.37(m,2H),2.98(t,J=13.2Hz,1H),2.68(M,3H),2.52-2.38(m,2H),1.96-1.82(m,3H),1.68(d,J=13.0Hz,2H),1.12(M,2H)。手性SFC A(45%MeOH):ee 100%,Rt=2.12min。

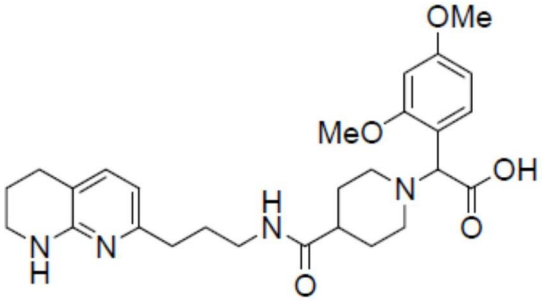
[1315] 化合物178-E2 LC/MS ESI 449.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.51(d,J=7.6Hz,2H),7.41(d,J=6.5Hz,3H),7.15(d,J=7.1Hz,1H),6.51(d,J=7.3Hz,1H),4.47(d,J=13.4Hz,2H),4.19(s,1H),3.86(M,4H),3.64-3.54(m,1H),3.42-3.37(m,2H),2.98(t,J=13.2Hz,1H),2.68(M,3H),2.62-2.38(m,2H),1.96-1.82(m,3H),1.68(d,J=13.0Hz,2H),1.12(M,2H)。手性SFC A(45%MeOH):ee 100%,Rt=3.57min。

[1316] 2-(4-(甲基(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁基)氨基)哌啶-1-基)乙酸(化合物179)

[1317] 

[1318] 化合物179 LC/MS ESI 361(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.15(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),3.41-3.37(m,2H),3.24(s,2H),2.78-2.63(m,6H),2.58-2.48(m,4H),2.39(s,3H),1.90(dd,J=11.1,6.5Hz,4H),1.83-1.55(m,7H)。

[1319] 2-(2,4-二甲氧基苯基)-2-(4-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基氨甲酰基)哌啶-1-基)乙酸(化合物180)

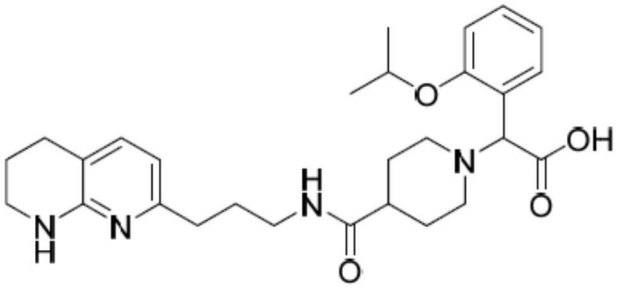
[1320] 

[1321] 化合物180LC/MS ESI 497(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.49(d,J=8.4Hz,1H),7.13(d,J=7.3Hz,1H),6.65-6.51(m,2H),6.38(t,J=6.3Hz,1H),4.71(s,1H),3.87(s,3H),3.82(d,J=6.3Hz,3H),3.40-3.36(m,2H),3.19(t,J=7.0Hz,2H),3.13(s,1H),2.71(dd,J=18.0,11.8Hz,3H),2.57-2.49(m,2H),2.35(s,1H),2.00(dd,J=22.2,11.0Hz,1H),1.98-1.73(m,8H)。

[1322] 2-(2-异丙氧基苯基)-2-(4-((3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)氨甲酰

基)哌啶-1-基)乙酸(对映异构化合物181-E1和181-E2)

[1323]

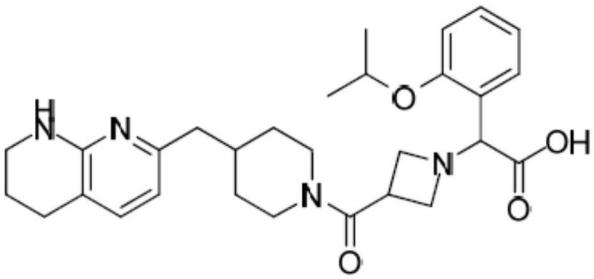


[1324] 化合物181-E1 LC/MS ESI 495(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.56(dd,J=7.7,1.4Hz,1H),7.45-7.36(m,1H),7.12(dd,J=18.8,7.8Hz,2H),7.00(t,J=7.5Hz,1H),6.38(d,J=7.3Hz,1H),4.96(s,1H),4.75(dt,J=12.1,6.0Hz,1H),3.71(s,1H),3.45-3.35(m,2H),3.33-3.25(m,2H),3.19(t,J=6.9Hz,2H),2.96(s,2H),2.70(t,J=6.2Hz,2H),2.57-2.49(m,2H),2.44(d,J=4.6Hz,1H),1.95(d,J=4.7Hz,4H),1.91-1.70(m,4H),1.42(d,J=6.0Hz,6H)。手性SFC F(45%MeOH):ee 97%,Rt=5.83min。

[1325] 化合物181-E2 LC/MS ESI 495(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.56(dd,J=7.7,1.5Hz,1H),7.41(dd,J=12.4,5.1Hz,1H),7.12(dd,J=16.5,7.8Hz,2H),7.01(t,J=7.5Hz,1H),6.38(d,J=7.3Hz,1H),4.98(s,1H),4.76(dt,J=12.1,6.0Hz,1H),3.41-3.35(m,2H),3.20(t,J=7.0Hz,2H),2.99(t,J=10.5Hz,1H),2.72(dd,J=18.3,12.0Hz,2H),2.57-2.50(m,2H),2.45(s,1H),2.12-1.92(m,4H),1.91-1.73(m,4H),1.42(d,J=6.0Hz,6H)。手性SFC F(45%MeOH):ee 94%,Rt=13.18min。

[1326] 2-(2-异丙氧基苯基)-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(对映异构化合物182-E1和182-E2)

[1327]

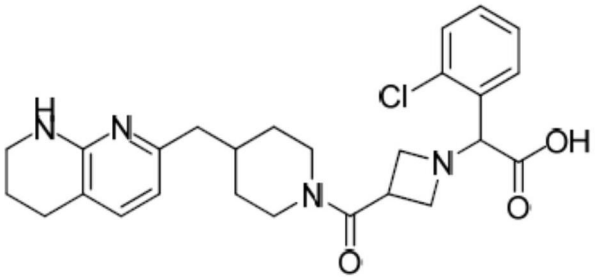


[1328] 化合物182-E1 LC/MS ESI 507.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.42-7.38(m,2H),7.14-7.09(m,2H),6.99(t,J=7.5Hz,2H),6.35-6.33(m,1H),5.13(d,J=9Hz,1H),4.78-4.52(m,1H),4.75-4.40(m,2H),4.21-4.14(m,2H),3.89-3.86(m,2H),3.57(d,J=15Hz,1H),3.39(t,J=5.5Hz,2H),3.03-2.98(m,1H),2.78-2.60(m,3H),2.46-2.45(m,2H),2.00-1.83(m,3H),1.71-1.68(m,2H),1.48-1.37(m,6H),1.14(s,2H)。手性HPLC L(70%EtOH):ee 100%,Rt=17.25min。

[1329] 化合物182-E2 LC/MS ESI 507.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.43-7.38(m,2H),7.15-7.10(m,2H),6.99(t,J=7.5Hz,2H),6.35-6.33(m,1H),5.14(d,J=9Hz,1H),4.79-4.52(m,1H),4.76-4.40(m,2H),4.21-4.13(m,2H),3.91-3.88(m,2H),3.57(d,J=15Hz,1H),3.39(t,J=5.5Hz,2H),3.03-2.98(m,1H),2.79-2.60(m,3H),2.46-2.45(m,2H),2.00-1.83(m,3H),1.71-1.68(m,2H),1.48-1.37(m,6H),1.14(s,2H)。手性HPLC L(70%

EtOH):ee 100%,Rt=22.66min。

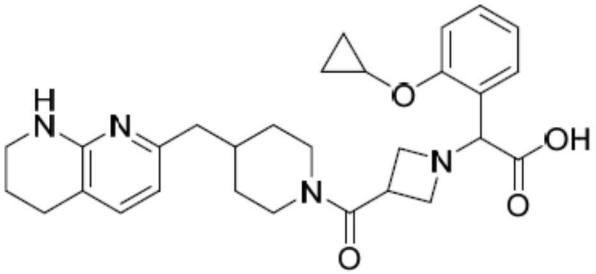
[1330] 2-(2-氯苯基)-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(对映异构化合物183-E1和183-E2)

[1331] 

[1332] 化合物183-E1 LC/MS ESI 483.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.63-7.57(m,1H),7.55-7.50(m,1H),7.42-7.35(m,2H),7.24(t,J=7.7Hz,1H),6.39(d,J=7.3Hz,1H),5.13(d,J=27.2Hz,1H),4.47(d,J=12.6Hz,1H),4.25(s,1H),4.08-3.73(m,4H),3.60(s,1H),3.45-3.37(m,2H),3.04-2.95(m,1H),2.73(t,J=6.2Hz,2H),2.68-2.42(m,3H),2.00-1.85(m,3H),1.79-1.62(m,2H),1.23-1.05(m,2H)。手性HPLC K(50%EtOH):ee 100%,Rt=12.44min。

[1333] 化合物183-E2 LC/MS ESI 483.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.64-7.58(m,1H),7.55-7.50(m,1H),7.42-7.35(m,2H),7.25(t,J=7.7Hz,1H),6.39(d,J=7.3Hz,1H),5.13(d,J=27.2Hz,1H),4.48(d,J=12.6Hz,1H),4.27(s,1H),4.09-3.75(m,4H),3.62(s,1H),3.45-3.37(m,2H),3.04-2.95(m,1H),2.73(t,J=6.2Hz,2H),2.68-2.42(m,3H),2.00-1.85(m,3H),1.79-1.62(m,2H),1.23-1.05(m,2H)。手性HPLC K(50%EtOH):ee 100%,Rt=22.79min。

[1334] 2-(2-环丙氧基苯基)-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(对映异构化合物184-E1和184-E2)

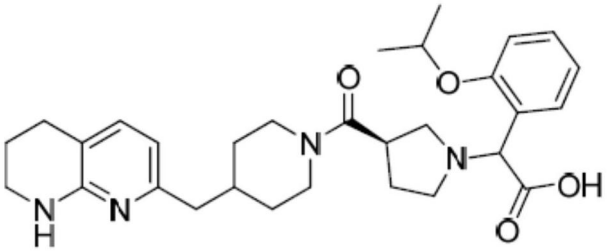
[1335] 

[1336] 化合物184-E1 LC/MS ESI 505(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.41(d,J=13.0Hz,3H),7.14(d,J=7.3Hz,1H),7.05(s,1H),6.35(d,J=7.2Hz,1H),5.00(s,1H),4.50-3.84(m,7H),3.55(s,1H),3.39(dd,J=11.4,5.7Hz,2H),3.00(t,J=13.2Hz,1H),2.70(dd,J=18.7,12.5Hz,3H),2.46(d,J=7.0Hz,2H),1.99-1.85(m,3H),1.69(d,J=12.6Hz,2H),1.15(d,J=11.2Hz,2H),1.04-0.75(m,4H)。手性H(45%MeOH):ee 100%,Rt=17.33min。

[1337] 化合物184-E2 LC/MS ESI 505(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.41(t,J=6.1Hz,3H),7.14(d,J=7.3Hz,1H),7.05(d,J=5.6Hz,1H),6.35(d,J=7.2Hz,1H),4.98(s,1H),4.49-3.82(m,7H),3.57(s,1H),3.39(dd,J=11.2,5.5Hz,2H),3.00(s,1H),2.70(dd,J=19.2,13.0Hz,3H),2.46(d,J=7.1Hz,2H),2.02-1.84(m,3H),1.69(d,J=12.6Hz,2H),1.14

(d,J＝12.4Hz,2H),0.99-0.74(m,4H)。手性H(45%MeOH):ee 99%,Rt＝22.42min。

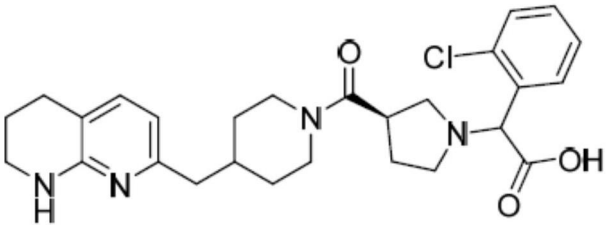
[1338] 2-(2-异丙氧基苯基)-2-((R)-3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)吡咯烷-1-基)乙酸(非对映异构化合物185-E1和185-E2)

[1339] 

[1340] 化合物185-E1 LC/MS ESI 521.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.53(d,J＝7.6Hz,1H),7.45-7.37(m,1H),7.14(d,J＝7.3Hz,1H),7.12-7.07(m,1H),7.04-6.95(m,1H),6.35(dd,J＝7.3,3.1Hz,1H),5.03(s,1H),4.81-4.72(m,1H),4.60(s,1H),4.48(d,J＝13.3Hz,1H),3.95-3.85(t,J＝23.5Hz,2H),3.61(s,1H),3.43-3.37(m,2H),3.28-3.17(m,2H),3.07(t,J＝13.2Hz,1H),2.72(t,J＝6.2Hz,2H),2.68-2.56(m,1H),2.50-2.31(m,3H),2.15-2.02(m,1H),2.00-1.85(m,3H),1.78-1.64(m,2H),1.48-1.38(m,6H),1.25-1.07(m,2H)。手性HPLC K(70%EtOH):ee 100%,Rt＝13.9min。

[1341] 化合物185-E2 LC/MS ESI 521.2(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.51(d,J＝7.0Hz,1H),7.40(t,J＝7.9Hz,1H),7.14(d,J＝7.2Hz,1H),7.09(d,J＝8.2Hz,1H),7.00(t,J＝7.5Hz,1H),6.35(dd,J＝7.3,3.8Hz,1H),5.09(s,1H),4.81-4.71(m,1H),4.50(d,J＝13.2Hz,1H),3.94(d,J＝13.3Hz,1H),3.66(s,1H),3.53-3.37(m,4H),3.19(s,1H),3.08(t,J＝12.9Hz,1H),2.72(t,J＝6.2Hz,2H),2.69-2.59(m,1H),2.51-2.31(m,3H),2.16-2.03(m,1H),2.01-1.84(m,3H),1.79-1.65(m,2H),1.48-1.35(m,6H),1.26-1.08(m,2H)。手性HPLC K(70%EtOH):ee 100%,Rt＝25.5min。

[1342] 2-(2-氯苯基)-2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)乙酸(非对映异构化合物186-E1和186-E2)

[1343] 

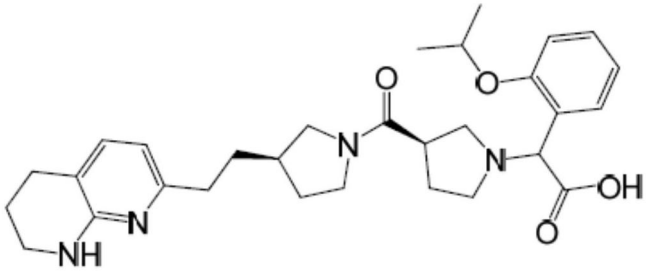
[1344] 化合物186-E1 LC/MS ESI 497.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.65(s,1H),7.42(s,1H),7.30(d,J＝3.9Hz,2H),7.04(d,J＝7.3Hz,1H),6.24(dd,J＝7.2,2.8Hz,1H),5.02(s,1H),4.35(d,J＝11.8Hz,1H),3.83(d,J＝12.9Hz,1H),3.48(s,3H),3.32-3.26(m,2H),3.15-2.88(m,3H),2.60(t,J＝6.1Hz,2H),2.57-2.46(m,1H),2.34(d,J＝3.5Hz,2H),2.29-2.17(m,1H),2.05-1.92(m,1H),1.88-1.74(m,3H),1.65-1.51(m,2H),1.12-0.96(m,2H)。手性SFC B(40%MeOH):ee 100%,Rt＝1.13min。

[1345] 化合物186-E2 LC/MS ESI 497.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.78(d,J＝3.7Hz,1H),7.52(d,J＝3.9Hz,1H),7.43-7.38(m,2H),7.15(d,J＝7.3Hz,1H),6.36(d,J＝7.2Hz,1H),5.18(s,1H),4.49(d,J＝12.8Hz,1H),3.98(d,J＝12.8Hz,1H),3.64(s,3H),

3.44-3.37(m,2H),3.14-2.98(m,3H),2.72(t,J=6.2Hz,2H),2.64(t,J=12.7Hz,1H),2.47(d,J=7.1Hz,2H),2.35-2.21(m,1H),2.17-2.04(m,1H),1.99-1.86(m,3H),1.78-1.65(m,2H),1.26-1.09(m,2H)。手性SFC B(40%MeOH):ee 86%,Rt=2.44min。

[1346] 2-(2-异丙氧基苯基)-2-((R)-3-((R)-3-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)吡咯烷-1-羰基)吡咯烷-1-基)乙酸(非对映异构化合物187-E1和187-E2)

[1347]

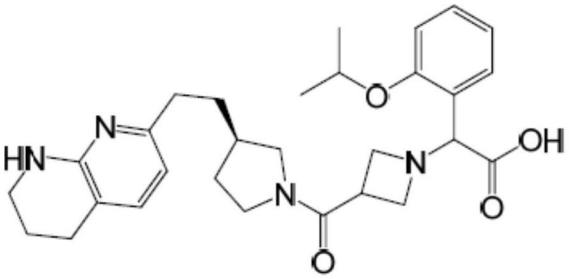


[1348] 化合物187-E1 LC/MS ESI 521.2(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.54(d,J=7.6Hz,1H),7.40(t,J=7.3Hz,1H),7.15(dd,J=7.3,4.3Hz,1H),7.10(d,J=8.4Hz,1H),7.00(t,J=7.5Hz,1H),6.40(dd,J=7.3,2.6Hz,1H),5.03(s,1H),4.81-4.72(m,1H),3.88-3.59(m,3H),3.55-3.37(m,4H),3.30-3.22(m,2H),3.15-2.95(m,1H),2.71(t,J=6.2Hz,2H),2.62-2.53(m,2H),2.40(td,J=15.8,8.1Hz,1H),2.30-2.06(m,3H),1.92-1.85(m,2H),1.75(dd,J=14.9,7.4Hz,2H),1.69-1.51(m,1H),1.44(dd,J=10.7,6.0Hz,6H)。手性SFC F(40%EtOH):ee 95%,Rt=7.8min。

[1349] 化合物187-E2 LC/MS ESI 521.2(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.43(d,J=7.5Hz,1H),7.35-7.30(m,1H),7.09-7.05(m,1H),7.01(d,J=8.3Hz,1H),6.92(t,J=7.5Hz,1H),6.32(dd,J=7.3,1.5Hz,1H),4.99(s,1H),4.68(dt,J=12.1,6.0Hz,1H),3.67-3.51(m,3H),3.46-3.29(m,5H),3.21-2.86(m,2H),2.64(t,J=6.2Hz,2H),2.55-2.46(m,2H),2.32(s,1H),2.23-1.98(m,3H),1.84-1.77(m,2H),1.68(dd,J=14.9,7.3Hz,2H),1.63-1.45(m,1H),1.35(dd,J=12.9,6.0Hz,6H)。手性SFC F(40%EtOH):ee 100%,Rt=9.6min。

[1350] 2-(2-异丙氧基苯基)-2-(3-((R)-3-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)吡咯烷-1-羰基)氮杂环丁烷-1-基)乙酸(非对映异构化合物188-E1和188-E2)

[1351]

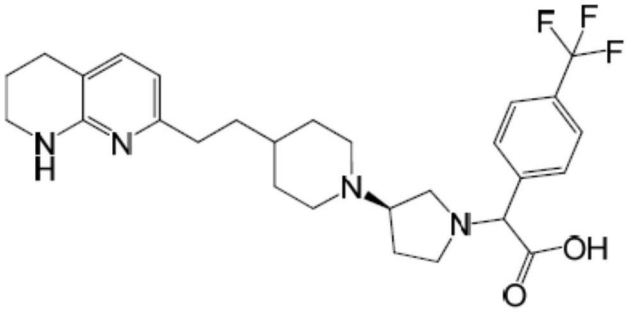


[1352] 化合物188-E1 LC/MS ESI 507.2(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.33(dd,J=16.8,7.8Hz,2H),7.07(d,J=7.3Hz,1H),7.03(d,J=8.4Hz,1H),6.92(t,J=7.5Hz,1H),6.32(dd,J=7.3,1.8Hz,1H),5.08(s,1H),4.69(dt,J=12.1,6.0Hz,1H),4.40-4.06(m,3H),3.86(s,1H),3.76-3.69(m,1H),3.58-3.40(m,2H),3.31(dt,J=12.8,4.8Hz,3H),2.97-2.89(m,1H),2.64(t,J=5.7Hz,2H),2.52-2.46(m,2H),2.18-1.99(m,2H),1.85-1.78(m,2H),1.70-1.64(m,2H),1.61-1.44(m,1H),1.40-1.34(m,6H)。手性SFC F(40%EtOH):ee

100%,Rt=9.14min

[1353] 化合物188-E2 LC/MS ESI 507.2(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.33(dd,J=14.6,7.7Hz,2H),7.08(d,J=4.7Hz,1H),7.03(d,J=8.3Hz,1H),6.92(t,J=7.5Hz,1H),6.33(d,J=6.1Hz,1H),5.09(s,1H),4.72-4.67(m,1H),4.39-4.07(m,3H),3.90-3.43(m,4H),3.34-3.26(m,3H),2.98-2.90(m,1H),2.64(t,J=6.1Hz,2H),2.49(d,J=5.9Hz,2H),2.11(d,J=39.5Hz,2H),1.82(s,2H),1.73-1.65(m,2H),1.53(d,J=38.0Hz,1H),1.37(dd,J=16.7,6.0Hz,6H)。手性SFCF(40%EtOH):ee 96%,Rt=11.57min

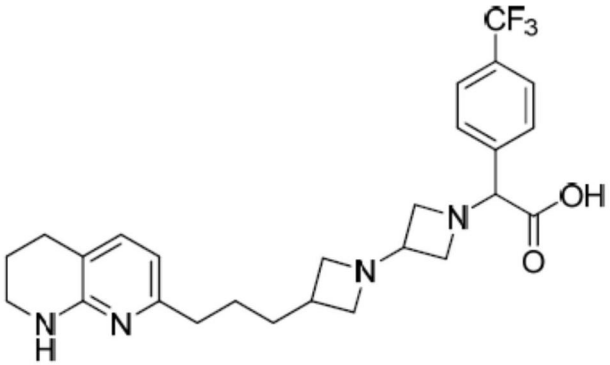
[1354] 2-((R)-3-(4-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)哌啶-1-基)-2-(4-(三氟甲基)苯基)乙酸(非对映异构化合物189-E1和189-E2)

[1355] 

[1356] 化合物189-E1 LC/MS ESI 517.0(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.63(d,J=8.2Hz,2H),7.55(d,J=8.2Hz,2H),7.08(d,J=7.5Hz,1H),6.32(d,J=7.3Hz,1H),3.87(s,1H),3.50(s,2H),3.34-3.26(m,3H),3.19-3.12(m,1H),2.64(dd,J=15.8,9.5Hz,6H),2.54-2.39(m,3H),2.12(s,1H),1.91(s,3H),1.80(dt,J=12.1,6.1Hz,2H),1.46(m,J=92.1Hz,5H)。手性SFC F(45%EtOH):ee 100%,Rt=9.14min。

[1357] 化合物189-E2 LC/MS ESI 517.0(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.63(d,J=8.2Hz,2H),7.56(d,J=8.2Hz,2H),7.07(d,J=7.3Hz,1H),6.31(d,J=7.3Hz,1H),3.89(s,1H),3.41(s,2H),3.34-3.28(m,2H),3.19(s,1H),3.00(s,1H),2.64(dd,J=19.8,13.7Hz,6H),2.50-2.40(m,3H),2.14(dd,J=13.5,4.9Hz,1H),1.96(dd,J=23.8,16.9Hz,3H),1.84-1.77(m,2H),1.55(dd,J=14.9,6.8Hz,2H),1.37(dd,J=41.3,26.8Hz,3H)。手性SFC F(45%EtOH):ee 100%,Rt=9.14min。

[1358] 2-(3-(3-(5,6,7,8-四氢-1,8-萘啶-2-基)丙基)-1,3'-二氮杂环丁烷-1'-基)-2-(4-(三氟甲基)苯基)乙酸(对映异构化合物190-E1和190-E2)

[1359] 

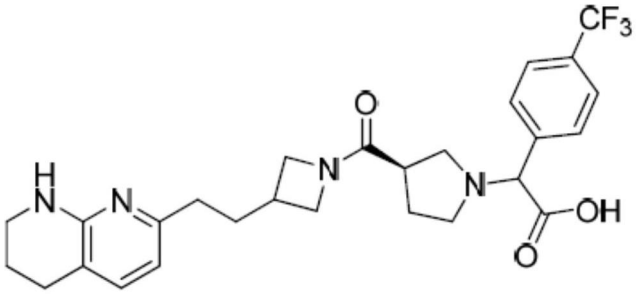
[1360] 化合物190-E1 LC/MS ESI 489.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.62(s,4H),7.28(d,J=7.3Hz,1H),6.43(d,J=7.3Hz,1H),4.26(s,2H),3.83(s,1H),3.70-3.48(m,4H),

3.39(dd,J=12.3,6.7Hz,3H),3.28(s,1H),3.14(s,1H),2.73(t,J=6.2Hz,3H),2.64-2.52(m,2H),1.92-1.85(m,2H),1.71-1.58(m,4H)。手性SFC B(40%MeOH):ee 100%,Rt=0.73min。

[1361] 化合物190-E2 LC/MS ESI 489.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.66(s,4H),7.18(d,J=7.6Hz,1H),6.39(d,J=7.3Hz,1H),4.29(s,1H),3.67(d,J=45.8Hz,4H),3.53-3.37(m,4H),3.23(s,3H),2.72(t,J=6.2Hz,2H),2.63(s,1H),2.53(t,J=6.7Hz,2H),1.93-1.84(m,2H),1.61(s,4H)。手性SFC B(40%MeOH):ee 100%,Rt=1.85min。

[1362] 2-((R)-3-(3-(2-(5,6,7,8-四氢-1,8-萘啶-2-基)乙基)氮杂环丁烷-1-羰基)吡咯烷-1-基)-2-(4-(三氟甲基)苯基)乙酸(非对映异构化合物191-E1和191-E2)

[1363]

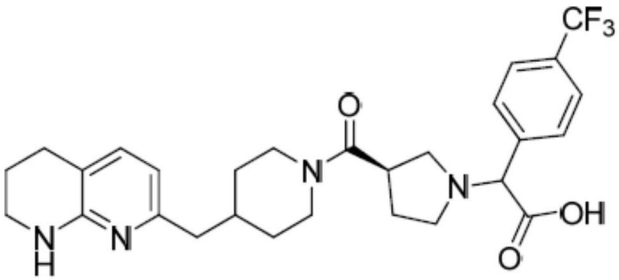


[1364] 化合物191-E1 LC/MS ESI 517.2$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.76-7.71(m,4H),7.20-7.18(m,1H),6.40-6.38(m,1H),4.41(s,1H),4.31-4.24(m,1H),4.07-4.00(m,1H),3.93(d,J=31.7Hz,1H),3.59-3.53(m,1H),3.48-3.34(m,3H),3.17(d,J=19.1Hz,2H),2.98(d,J=41.3Hz,2H),2.72(t,J=6.1Hz,2H),2.68-2.59(m,1H),2.56-2.48(m,2H),2.24(d,J=7.2Hz,1H),2.08(s,1H),1.96-1.90(m,4H)。手性HPLC J(30%EtOH):ee 100%,Rt=13.53min。

[1365] 化合物191-E2 LC/MS ESI 517.2$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.79-7.72(m,4H),7.22-7.18(m,1H),6.43-6.38(m,1H),4.42(s,1H),4.33-4.24(m,1H),4.08-4.00(m,1H),3.94(d,J=31.7Hz,1H),3.62-3.53(m,1H),3.49-3.34(m,3H),3.18(d,J=19.1Hz,2H),2.99(d,J=41.3Hz,2H),2.73(t,J=6.1Hz,2H),2.69-2.59(m,1H),2.57-2.48(m,2H),2.24(d,J=7.2Hz,1H),2.09(s,1H),1.97-1.90(m,4H)。手性HPLC J(30%EtOH):ee 100%,Rt=24.12min。

[1366] 2-((R)-3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)吡咯烷-1-基)-2-(4-(三氟甲基)苯基)乙酸(非对映异构化合物192-E1和192-E2)

[1367]

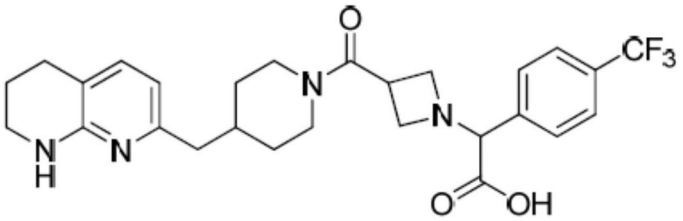


[1368] 化合物192-E1 LC/MS ESI 531.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.74(t,J=7.6Hz,2H),7.64-7.57(m,2H),7.12(t,J=6.8Hz,1H),6.33(dd,J=16.2,7.3Hz,1H),4.46(d,J=12.6Hz,1H),3.97(d,J=12.5Hz,1H),3.82(d,J=12.1Hz,1H),3.42-3.37(m,2H),

3.15(s,1H),3.04-2.93(m,1H),2.77-2.72(m,3H),2.57(dd,J=23.6,12.7Hz,1H),2.49-2.36(m,4H),2.15-2.01(m,3H),1.89(dd,J=11.3,5.8Hz,3H),1.72-1.61(m,2H),1.20-0.99(m,2H)。手性SFC B(35%MeOH):ee 100%,Rt=1.27min。

[1369] 化合物192-E2 LC/MS ESI 531.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.73(s,2H),7.62-7.57(m,2H),7.14(d,J=7.7Hz,1H),6.35(t,J=6.7Hz,1H),4.49(s,1H),4.04(d,J=13.9Hz,1H),3.79(d,J=5.7Hz,1H),3.39(dd,J=11.7,6.0Hz,3H),3.19(s,1H),3.05(s,1H),2.72(t,J=6.1Hz,2H),2.63-2.52(m,2H),2.45(t,J=7.6Hz,4H),2.02(s,2H),1.96(s,1H),1.92-1.87(m,2H),1.68(d,J=16.6Hz,2H),1.12(s,2H)。手性SFC B(35%MeOH):ee 100%,Rt=4.19min。

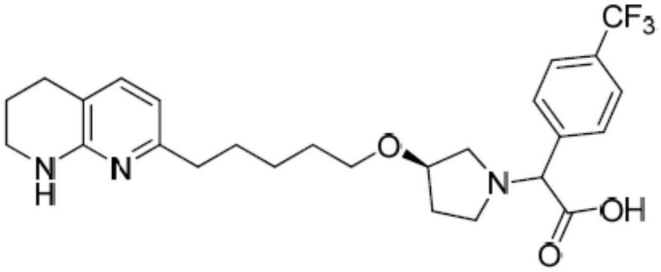
[1370] 2-(3-(4-((5,6,7,8-四氢-1,8-萘啶-2-基)甲基)哌啶-1-羰基)氮杂环丁烷-1-基)-2-(4-(三氟甲基)苯基)乙酸(对映异构化合物193-E1和193-E2)

[1371] 

[1372] 化合物193-E1 LC/MS ESI 517.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.72(dd,J=20.3,8.1Hz,4H),7.26(d,J=6.2Hz,1H),6.41(d,J=7.2Hz,1H),4.64(s,1H),4.49(d,J=13.1Hz,1H),4.22(s,1H),3.91(d,J=67.7Hz,4H),3.61(d,J=12.8Hz,1H),3.41(s,2H),3.00(t,J=13.1Hz,1H),2.74(t,J=6.2Hz,2H),2.65(t,J=11.7Hz,1H),2.57-2.46(m,2H),1.98-1.87(m,3H),1.69(d,J=10.7Hz,2H),1.16(d,J=11.3Hz,2H)。手性SFC B(35%MeOH):ee 100%,Rt=0.93min。

[1373] 化合物193-E2 LC/MS ESI 517.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.72(dd,J=19.2,8.2Hz,4H),7.26(s,1H),6.42(d,J=7.3Hz,1H),4.62(s,1H),4.49(d,J=13.0Hz,1H),4.20(s,1H),3.83(s,4H),3.61(d,J=13.8Hz,1H),3.42(s,2H),3.00(t,J=13.0Hz,1H),2.75(t,J=6.2Hz,2H),2.65(t,J=11.7Hz,1H),2.51(d,J=7.0Hz,2H),1.99-1.87(m,3H),1.70(s,2H),1.17(d,J=11.8Hz,2H)。手性SFC B(35%MeOH):ee 100%,Rt=3.78min。

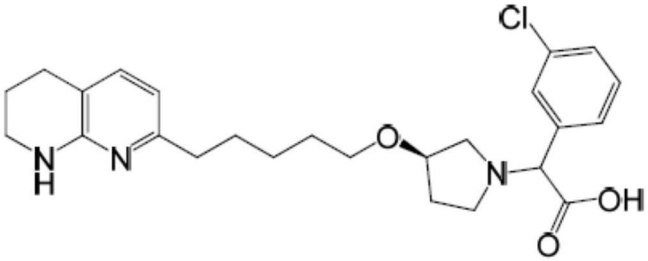
[1374] 2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氧基)吡咯烷-1-基)-2-(4-(三氟甲基)苯基)乙酸(非对映异构化合物194-E1和194-E2)

[1375] 

[1376] 化合物194-E1 LC/MS ESI 492.1$(M+H)^+$。^{1}H NMR(500MHz,MeOD)δ7.81-7.69(m,4H),7.22(d,J=7.3Hz,1H),6.42(d,J=7.3Hz,1H),4.54(s,1H),4.17(s,1H),3.49-3.36(m,5H),3.21(s,1H),3.12(s,1H),2.93(s,1H),2.72(t,J=6.2Hz,2H),2.58(t,J=7.8Hz,2H),2.13-2.08(m,2H),1.93-1.85(m,2H),1.78-1.56(m,4H),1.54-1.39(m,2H)。

[1377] 化合物194-E2 LC/MS ESI 492.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.81-7.70(m,4H),7.31(d,J=7.1Hz,1H),6.45(d,J=7.2Hz,2H),4.19-4.12(m,2H),3.53-3.37(m,5H),2.90(s,1H),2.81-2.67(m,5H),2.64-2.53(m,1H),2.31-2.17(m,1H),2.00-1.85(m,3H),1.84-1.62(m,3H),1.60-1.41(m,3H)。

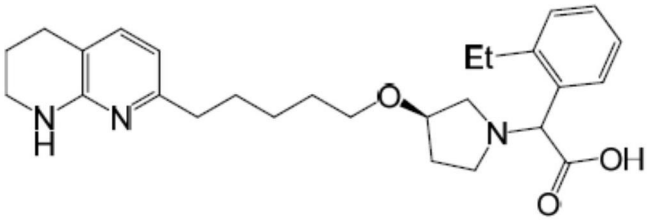
[1378] 2-(3-氯苯基-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氧基)吡咯烷-1-基)乙酸(非对映异构化合物195-E1和195-E2)

[1379] 

[1380] 化合物195-E1 LC/MS ESI 458.1(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.52(s,1H),7.37(dd,J=6.7,1.9Hz,1H),7.35-7.30(m,2H),7.09(d,J=7.3Hz,1H),6.29(d,J=7.3Hz,1H),4.35(s,1H),4.06(s,1H),3.32(ddd,J=29.1,13.4,8.3Hz,5H),3.15(d,J=9.0Hz,1H),3.00(d,J=12.2Hz,1H),2.90-2.81(m,1H),2.61(t,J=6.2Hz,2H),2.45(t,J=7.7Hz,2H),1.99(dd,J=12.0,8.5Hz,2H),1.82-1.74(m,2H),1.63-1.48(m,4H),1.39-1.28(m,2H)。

[1381] 化合物195-E2 LC/MS ESI 458.1(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.56(s,1H),7.39(dd,J=5.3,2.4Hz,1H),7.28(dd,J=4.8,1.4Hz,2H),7.17(d,J=7.4Hz,1H),6.32(d,J=7.3Hz,1H),4.03(d,J=17.6Hz,2H),3.39-3.26(m,5H),2.76(d,J=65.3Hz,3H),2.65-2.52(m,3H),2.50-2.43(m,1H),2.12(dd,J=13.8,6.8Hz,1H),1.88(s,1H),1.77(dd,J=11.4,6.1Hz,2H),1.70-1.50(m,3H),1.49-1.29(m,3H)。

[1382] 2-(2-乙基苯基-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氧基)吡咯烷-1-基)乙酸(非对映异构化合物196-E1和196-E2)

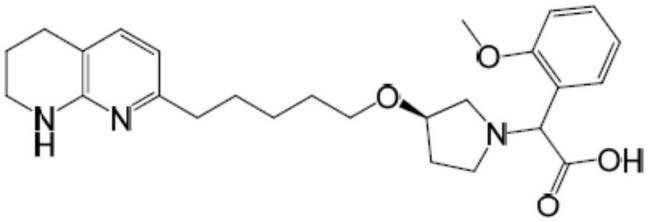
[1383] 

[1384] 化合物196-E1 LC/MS ESI 452.2.1(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.51(d,J=7.7Hz,1H),7.26-7.21(m,2H),7.19-7.13(m,1H),7.03(d,J=7.3Hz,1H),6.27(d,J=7.3Hz,1H),4.11(s,1H),3.51-3.36(m,3H),3.31-3.26(m,2H),3.16(d,J=12.6Hz,1H),2.94(s,2H),2.76(ddd,J=14.9,7.4,2.9Hz,2H),2.60(t,J=6.3Hz,2H),2.44(t,J=7.5Hz,2H),2.07-1.90(m,2H),1.78(dt,J=12.3,6.2Hz,2H),1.60-1.32(m,7H),1.23(t,J=7.6Hz,3H)。

[1385] 化合物196-E2 LC/MS ESI 452.2.1(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.56(d,J=7.8Hz,1H),7.22(q,J=5.2Hz,2H),7.18-7.14(m,1H),7.07(d,J=7.3Hz,1H),6.28(d,J=7.3Hz,1H),4.67(s,1H),4.05(s,1H),3.43-3.26(m,5H),3.15-3.00(m,3H),2.79(ddt,J=

22.1,14.7,7.3Hz,2H),2.61(t,J=6.3Hz,2H),2.50-2.41(m,2H),2.05(s,2H),1.82-1.75(m,2H),1.63-1.46(m,4H),1.35(dd,J=14.7,8.2Hz,2H),1.22(t,J=7.6Hz,3H)。

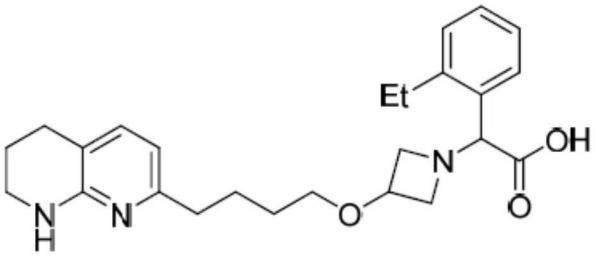
[1386] 2-(2-甲氧基苯基)-2-((R)-3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氧基)吡咯烷-1-基)乙酸(非对映异构化合物197-E1和197-E2)

[1387] 

[1388] 化合物197-E1 LC/MS ESI 454.2.1(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.41(d,J=7.3Hz,1H),7.35(ddd,J=8.4,7.5,1.7Hz,1H),7.03(dd,J=13.5,7.7Hz,2H),6.97-6.93(m,1H),6.29(d,J=7.3Hz,1H),4.94(s,1H),4.10(s,1H),3.82(d,J=4.0Hz,3H),3.54-3.28(m,5H),3.17(d,J=13.0Hz,1H),3.00(ddd,J=11.5,8.1,3.5Hz,1H),2.61(t,J=6.3Hz,2H),2.45(dd,J=8.2,6.3Hz,2H),2.07-1.93(m,2H),1.83-1.75(m,2H),1.58(ddd,J=14.0,12.9,7.5Hz,4H),1.39-1.30(m,2H)。手性SFC F(45%EtOH):ee 100%,Rt=2.41min。

[1389] 化合物197-E2 LC/MS ESI 454.2.1(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.45(d,J=7.5Hz,1H),7.36-7.29(m,1H),7.06(d,J=7.3Hz,1H),7.01(d,J=8.2Hz,1H),6.93(t,J=7.5Hz,1H),6.29(d,J=7.3Hz,1H),4.87(s,1H),4.07(s,1H),3.80(d,J=10.1Hz,3H),3.48-3.26(m,6H),3.17-3.05(m,2H),2.61(t,J=6.2Hz,2H),2.50-2.41(m,2H),2.14-1.97(m,2H),1.82-1.76(m,2H),1.62-1.46(m,4H),1.40-1.28(m,2H)。手性SFC F(45%EtOH):ee 99%,Rt=3.8min。

[1390] 2-(2-乙基苯基)-2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)氮杂环丁烷-1-基)乙酸(对映异构化合物198-E1和198-E2)

[1391] 

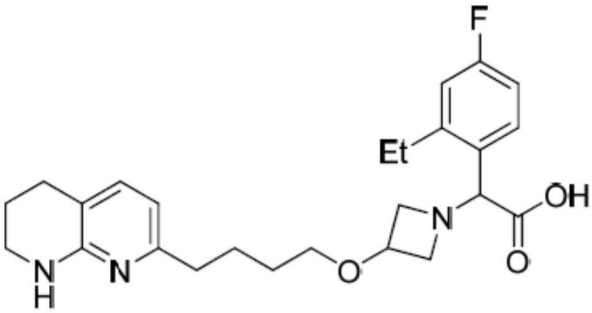
[1392] 化合物198-E1 LC/MS ESI 424.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.43(d,J=7.7Hz,1H),7.32(dd,J=7.3,5.5Hz,2H),7.26-7.21(m,1H),7.17(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),5.01(s,1H),4.29(d,J=4.8Hz,2H),3.97(s,1H),3.81(s,1H),3.62(s,1H),3.46-3.40(m,4H),2.97-2.92(m,2H),2.72(t,J=6.2Hz,2H),2.56(t,J=7.6Hz,2H),1.92-1.86(m,2H),1.76-1.70(m,2H),1.64-1.57(m,2H),1.34(t,J=7.6Hz,3H)。手性HPLC K(50%EtOH):ee 100%,Rt=5.40min。

[1393] 化合物198-E2 LC/MS ESI 424.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.44(d,J=7.8Hz,1H),7.34-7.28(m,2H),7.25-7.16(m,2H),6.39(d,J=7.3Hz,1H),4.99(s,1H),4.28(d,J=5.2Hz,2H),3.95(s,1H),3.76(d,J=4.8Hz,1H),3.56(d,J=9.5Hz,1H),3.45-3.40

(m,4H),2.96-2.90(m,2H),2.71(t,J=6.2Hz,2H),2.56(t,J=7.6Hz,2H),1.91-1.83(m,2H),1.75-1.65(m,2H),1.64-1.54(m,2H),1.34(t,J=7.6Hz,3H)。手性HPLC K(50%EtOH):ee 100%,Rt=7.56min。

[1394] 2-(2-乙基-4-氟苯基)-2-(3-(4-(5,6,7,8-四氢-1,8-萘啶-2-基)丁氧基)氮杂环丁烷-1-基)乙酸(对映异构化合物199-E1和199-E2)

[1395]

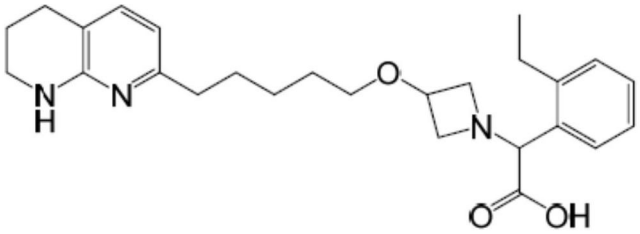


[1396] 化合物199-E1 LC/MS ESI 442.3(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.47(dd,J=8.5,5.9Hz,1H),7.18(d,J=7.3Hz,1H),7.06(dd,J=10.2,2.4Hz,1H),6.99-6.91(m,1H),6.39(d,J=7.3Hz,1H),4.87(s,1H),4.30-4.17(m,2H),3.89(s,1H),3.69(d,J=5.4Hz,1H),3.52(s,1H),3.45-3.40(m,4H),2.95-2.90(m,2H),2.71(t,J=6.2Hz,2H),2.56(t,J=7.6Hz,2H),1.91-1.84(m,2H),1.75-1.67(m,2H),1.62-1.55(m,2H),1.33(t,J=7.5Hz,3H)。手性SFC B(20%MeOH):ee 100%,Rt=1.96min

[1397] 化合物199-E2 LC/MS ESI 442.3(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.49(dd,J=8.5,5.9Hz,1H),7.20(d,J=7.3Hz,1H),7.08(dd,J=10.2,2.4Hz,1H),7.01-6.91(m,1H),6.39(d,J=7.3Hz,1H),4.89(s,1H),4.35-4.19(m,2H),3.90(s,1H),3.72(d,J=5.4Hz,1H),3.52(s,1H),3.45-3.42(m,4H),2.98-2.90(m,2H),2.74(t,J=6.2Hz,2H),2.57(t,J=7.6Hz,2H),1.93-1.84(m,2H),1.79-1.67(m,2H),1.68-1.55(m,2H),1.35(t,J=7.5Hz,3H)。手性SFC B(20%MeOH):ee 100%,Rt=3.19min。

[1398] 2-(2-乙基苯基)-2-(3-(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊氧基)氮杂环丁烷-1-基)乙酸(对映异构化合物200-E1和200-E2)

[1399]

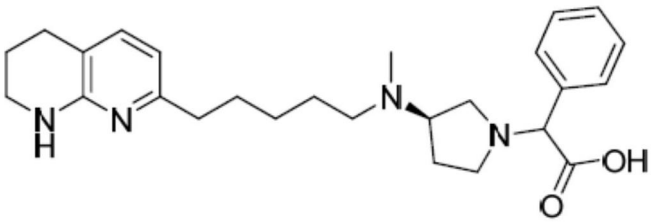


[1400] 化合物200-E1 LC/MS ESI 438.3(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.33(d,J=7.7Hz,1H),7.28-7.24(m,2H),7.18-7.14(m,1H),7.06(d,J=7.3Hz,1H),6.28(d,J=7.3Hz,1H),4.98(s,1H),4.23(s,2H),3.93(s,1H),3.76(s,1H),3.60(s,1H),3.37-3.32(m,2H),3.32-3.29(m,2H),2.90-2.82(m,2H),2.62(d,J=6.2Hz,2H),2.44(t,J=7.6Hz,2H),1.83-1.77(m,2H),1.61-1.51(m,4H),1.37-1.32(m,2H),1.27(t,J=7.6Hz,3H)。手性SFC F(60%MeOH):ee 100%,Rt=2.96min。

[1401] 化合物200-E2 LC/MS ESI 438.3(M+H)+。^{1}H NMR(500MHz,MeOD)δ7.33(d,J=7.7Hz,1H),7.28-7.24(m,2H),7.18-7.13(m,1H),7.06(d,J=7.3Hz,1H),6.28(d,J=

7.3Hz,1H),4.97(s,1H),4.22(dd,J=11.2,5.7Hz,2H),3.93(d,J=10.4Hz,1H),3.75(d,J=6.4Hz,1H),3.59(d,J=10.6Hz,1H),3.38-3.27(m,4H),2.84(dq,J=22.2,7.4Hz,2H),2.62(t,J=6.3Hz,2H),2.44(t,J=7.7Hz,2H),1.84-1.76(m,2H),1.60-1.49(m,4H),1.33(dd,J=15.4,8.2Hz,2H),1.27(t,J=7.6Hz,3H)。手性SFC F(60%MeOH):ee 98%,Rt=4.89min。

[1402] 2-((R)-3-(甲基(5-(5,6,7,8-四氢-1,8-萘啶-2-基)戊基)氨基)吡咯烷-1-基)-2-苯基乙酸(非对映异构化合物201-E1和201-E2)

[1403] 

[1404] 化合物201-E1 LC/MS ESI 437.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.53(d,J=6.6Hz,2H),7.37-7.30(m,3H),7.17(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.05(s,1H),3.48-3.42(m,1H),3.41-3.37(m,2H),3.19(s,1H),2.91(s,1H),2.78(d,J=6.8Hz,2H),2.71(dd,J=16.2,10.0Hz,3H),2.62-2.49(m,6H),2.16(dd,J=13.3,5.1Hz,1H),2.00(dd,J=13.5,5.9Hz,1H),1.92-1.86(m,2H),1.71-1.59(m,4H),1.38(dt,J=14.2,7.3Hz,2H)。

[1405] 化合物201-E2 LC/MS ESI 437.1(M+H)$^+$。^{1}H NMR(500MHz,MeOD)δ7.55(d,J=6.5Hz,2H),7.39-7.31(m,3H),7.19(d,J=7.3Hz,1H),6.39(d,J=7.3Hz,1H),4.05(s,1H),3.43(d,J=6.3Hz,1H),3.40-3.36(m,2H),3.19(s,1H),2.79(s,4H),2.72(t,J=6.2Hz,2H),2.65-2.59(m,1H),2.56(t,J=7.7Hz,2H),2.46(s,3H),2.13(dd,J=13.3,7.7Hz,1H),1.96-1.85(m,3H),1.74-1.56(m,4H),1.41(p,J=7.4Hz,2H)。

[1406] 实例34:用于αvβ6结合的化合物的荧光偏振检定

[1407] 使用荧光偏振(FP)检定来通过与荧光素标记肽GRGDLGRL的结合竞争性来测量化合物活性。于所述检定中,利用含于以下中的测试化合物培育10nM整合蛋白αvβ6:2mM氯化锰、0.1mM氯化钙、pH 7.3的20mM HEPES缓冲液、150mM氯化钠、0.01%Triton X-100、2% DMSO和3nM荧光素标记肽。于384-孔盘中运行所述检定。针对两个检定版本,在22℃下,将整合蛋白用测试化合物预培育15分钟,然后添加荧光素标记肽。于添加荧光素标记肽后,将所述检定在22℃下培育1小时和测量荧光偏振。通过非线性回归、4-参数曲线拟合来确定IC_{50}值(图1)。

[1408] 以引用的方式并入

[1409] 本文中引用的所有美国专利和美国专利申请公开案以引用的方式并入本文中。

[1410] 等效物

[1411] 所属领域的技术人员仅仅使用常规实验,将知晓或能确定本文中所述的本发明的特定实施例的许多等效物。这些等效物旨在由下列权利要求书涵盖。

化合物	αvβ6 IC_{50}	化合物	αvβ6 IC_{50}	化合物	αvβ6 IC_{50}
3	A	43	B	72	C
4	B	44-E1	C	73	C
5	B	44-E2	C	74	C
6	C	45-E1	B	75	C
7-E2	C	45-E2	C	77	B
8-E1	B	46-E1	C	78	B
9	C	46-E2	C	79	C
10-E1	B	47	C	80	C
10-E2	C	48-E1	B	82	C
11-E1	A	50-E1	C	83	C
11-E2	C	50-E2	C	85	C
12-E1	B	51-E1	C	86	C
12-E2	C	51-E2	C	88	C
13-E1	B	52	B	90	C
13-E2	A	53-E2	C	91	B
14	A	54-E1	B	92	C
15	A	54-E2	B	93	C
16	B	55-E1	C	94	B
17	B	56-E1	C	95	B
18	B	56-E2	B	97	C
19	B	57	C	99	C
20	B	60	C	101	C
21	B	61	B	102	B
22	A	62-E1	B	103	C
23-E1	C	62-E2	B	107	C
23-E2	C	63	C	110	C
24-E1	B	64	C	111	B
24-E2	B	65	B	112	B
25	A	66	C	113	B
26	C	67	B	118	C
27	B	68	B	121	C
28	B	69	C	123	C
41	C	70	B	125	C
42	C	71	C		

αvβ6 IC_{50}：A：IC_{50}<0.1 μM；B：0.1 μM<IC_{50}<1 μM；C：1 μM<IC_{50}<10 μM。

图1

化合物	αvβ6 IC_{50}	化合物	αvβ6 IC_{50}	化合物	αvβ6 IC_{50}
129-E1	A	154-E1	A	178-E2	B
129-E2	C	154-E2	B	179	B
130-E2	B	155-E1	B	180	B
131-E1	A	155-E2	A	181-E1	B
131-E2	C	156-E1	A	181-E2	C
132-E1	B	156-E2	C	182-E1	A
132-E2	B	157-E1	A	182-E2	B
133	A	157-E2	C	183-E1	B
134-E1	C	158-E1	C	183-E2	A
134-E2	B	158-E2	B	184-E1	A
135-E1	A	159-E1	B	184-E2	A
135-E2	C	160-E1	A	185-E1	B
136-E1	A	160-E2	C	185-E2	A
136-E2	B	161-E1	C	186-E1	C
137-E1	A	161-E2	A	186-E2	A
137-E2	C	162-E1	C	187-E1	B
138-E1	A	162-E2	A	187-E2	A
138-E2	C	163-E1	C	188-E1	A
139-E1	B	163-E2	A	188-E2	B
139-E2	C	164-E1	B	189-E1	C
140-E1	B	164-E2	C	189-E2	A
140-E2	C	165-E1	A	190-E1	C
141-E1	C	165-E2	C	190-E2	B
141-E2	B	166-E1	B	191-E1	A
142	B	166-E2	A	191-E2	A
143	B	167-E1	A	192-E1	C
144-E1	C	167-E2	B	192-E2	B
144-E2	B	168	A	193-E1	B
145	A	169	A	193-E2	B
146-E1	A	170-E1	A	194-E1	A
146-E2	C	170-E2	A	194-E2	C
147-E1	A	171-E1	B	195-E1	A
147-E2	C	171-E2	A	195-E2	B
148-E1	C	172-E1	B	196-E1	A
148-E2	B	172-E2	A	196-E2	C
149-E1	A	173-E1	A	197-E1	A
149-E2	A	173-E2	C	197-E2	B
150	A	174	A	198-E1	C
151-E1	A	175-E1	C	198-E2	A
151-E2	B	175-E2	A	199-E1	C
152-E1	A	176-E2	B	199-E2	A
152-E2	B	177-E1	B	200-E2	B
153-E1	A	177-E2	A	201-E1	B
153-E2	C	178-E1	B	201-E2	C

αvβ6 IC_{50}：A：IC_{50}<0.1 μM；B：0.1 μM<IC_{50}<1 μM；C：1 μM<IC_{50}<10 μM。

图1(续)