说明书

发明名称: 用于自身免疫疾病治疗的S1PR4调节剂化合物及其应用

技术领域

[0001] 本发明涉及药学领域。具体地说，本发明涉及S1PR4调节剂用于预防和治疗自身免疫疾病的新型化合物及其应用。

背景技术

[0002] 鞘氨醇-1-磷酸(S1P)可以介导生物学信号传递到生物膜上的G蛋白偶联受体或者直接作用于胞内受体，从而在介导炎症反应、过敏反应以及参与免疫细胞的迁移、增殖和分化等方面发挥特殊作用。S1P信号的异常调节与自身免疫疾病、心血管疾病、神经系统性疾病以及癌症等有关。作为G蛋白偶联受体家族成员之一，目前在哺乳动物中发现5种不同的S1P受体亚型，分别是S1PR1、S1PR2、S1PR3、S1PR4和S1PR5(旧称为EDG1、EDG5、EDG3、EDG6和EDG8)。其中S1PR1、S1PR2和S1PR3广泛表达于各种机体组织，S1PR4则主要在淋巴系统和血液系统中集中表达，S1PR5主要在中枢神经系统中表达。目前研究证实S1P可通过与细胞表面的S1PR1结合，活化β-arrestin信号传导途径使受体内陷，进而诱导淋巴细胞回巢，抑制淋巴细胞从外周淋巴结及次级淋巴器官向外部转移，从而达到阻止淋巴细胞向炎症部位转移的效果，具有很好的免疫抑制调控作用。靶向调控S1PR1信号通路可以实现对多种自身免疫性疾病的调节，如系统性红斑狼疮、溃疡性结肠炎、克罗恩病、多发性硬化症、类风湿性关节炎、银屑病、强直性脊柱炎等。但是目前针对S1PR1为靶点的上市药物对S1PR其他亚型具有较好的激动活性，缺乏选择性，尤其是S1PR3的激活会导致心动过缓等脱靶副作用，因此开发选择性S1PRs激动剂具有重要意义。

[0003] 然而目前有关S1PR4选择性药物的报道较少，已披露的S1PR4激动剂/拮抗剂几乎全部由美国Scripps研究所的Edward Roberts开发，但是这些S1PR4调节剂仅作为体外工具分子进行探讨，并没有系统的机制研究和成药性评价。因此开发口服有效的选择性S1PR4激动剂/拮抗剂，应用于自体免疫性疾病的治疗是有重要科学价值。

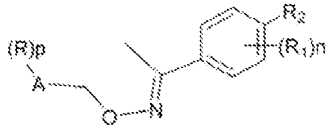
[0004] 发明内容

[0005] 本发明的目的是提供相关化合物作为S1PR调节剂，特别是S1PR4激动剂。

[0006] 本发明的另一目的是提供包含上述化合物的药物组合物。

[0007] 本发明还有一目的是提供上述化合物或药物组合物在制备治疗S1PR4相关疾病或调节S1P受体的药物中的用途。

[0008] 在第一方面，本发明提供式I所示的化合物、或其旋光异构体或药学上可接受的盐：



I

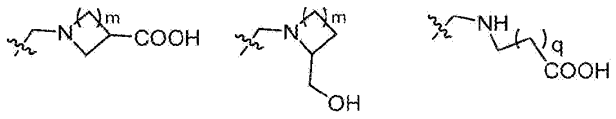
[0009] A选自取代或未取代的C_5-C_8芳环(例如苯基)或C_8-C_{14}稠芳环(例如萘基)、取代或未取代的含有1-3个选自N或O的杂原子的五元或六元杂环基；

[0010] R独立选自下组：氢、卤素、氰基、取代或未取代的C_1-C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3-C_8环烷基或环烯基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_5-C_8芳基(例如苯基)、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的C_5-C_8芳基甲酰基，p为1-3的整数；

[0011] R^1选自下组：氢、卤素、氰基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_1-C_{10}烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_6链烯基、取代或未取代的C_3-C_6环烯基、取代或未取代的C_3-C_8内酯基、取代或未取代的C_1-C_{10}酰胺基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基、取代或未取代的C_5-C_8芳杂环基；

[0012] n选自1-3整数；

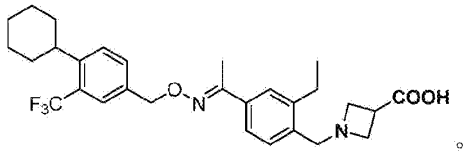
[0013] R^2选自下组：



[0014] m选自1-4整数；

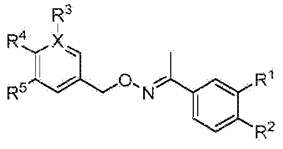
[0015] q选自1-2整数。

[0016] 在优选的实施方式中，所述化合物不是以下化合物：



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[0017] 在具体的实施方式中，所述化合物如下式II所示，

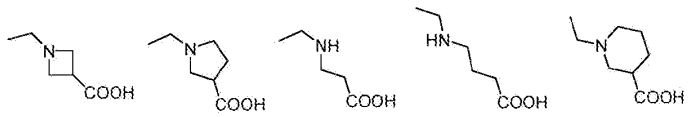


II

[0018] 式中，

[0019] R^1选自下组：氢、卤素(优选F、Cl或Br)、氰基、取代或未取代的C_1-C_5烷氧基(优选甲氧基)、取代或未取代的C_1-C_{10}烷基(优选取代或未取代的C_1-C_6烷基，例如，甲基、乙基、三氟甲基)、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_6链烯基、取代或未取代的C_3-C_6环烯基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基、取代或未取代的C_5-C_8芳杂环基；

[0020] R^2选自下组：



[0021] X选自：C或N；

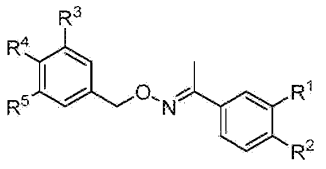
[0022] R^3不存在或是选自下组的取代基：氢、氰基、卤素、取代或未取代的C_1-C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3-C_8环烷基、氰基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的C_5-C_8芳基甲酰基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基；

[0023] R^5选自下组：氢、氰基、卤素、取代或未取代的C_1-C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3-C_8环烷基、氰基、取代或未取代的C_1-

C_5烷氧基、取代或未取代的C_1−C_{10}烷基甲酰基、取代或未取代的C_5−C_8芳基甲酰基、取代或未取代的C_5−C_8芳基、取代或未取代的含有1−2个选自N、O或S的杂原子的五元或六元杂环基；

[0024] R^4选自下组：氢、卤素、取代或未取代的C_1−C_{10}烷基、取代或未取代的C_3−C_8环烷基或环烯基、取代或未取代的C_5−C_8芳基、取代或未取代的含有1−2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基、取代或未取代的C_1−C_{10}烷基甲酰基、取代或未取代的芳基甲酰基。

[0025] 在具体的实施方式中，所述化合物如下式Ⅲ所示，

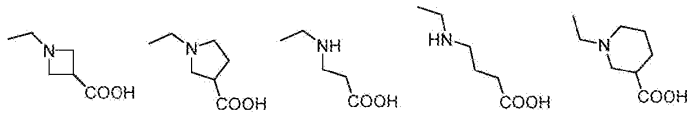


III

[0026] 式中，

[0027] R^1选自下组：氢、卤素(优选F、Cl或Br)、氰基、取代或未取代的C_1−C_5烷氧基(优选甲氧基)、取代或未取代的C_1−C_{10}烷基(优选取代或未取代的C_1−C_6烷基，例如，甲基、乙基、三氟甲基)、取代或未取代的C_3−C_8环烷基、取代或未取代的C_2−C_6链烯基、取代或未取代的C_3−C_6环烯基、取代或未取代的C_5−C_8芳基、取代或未取代的含有1−2个选自N、O或S的杂原子的五元或六元杂环基、取代或未取代的C_5−C_8芳杂环基；

[0028] R^2选自下组：

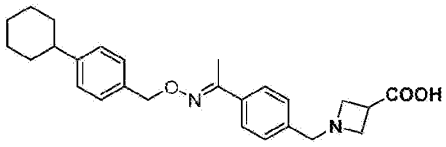
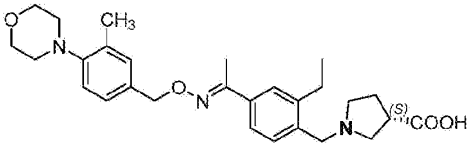
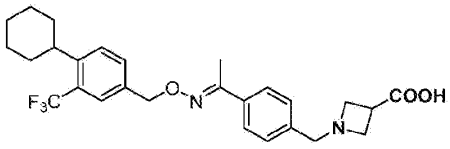
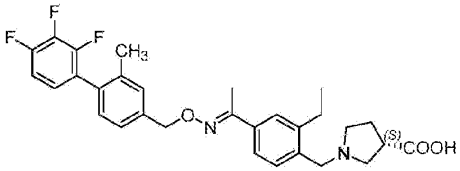
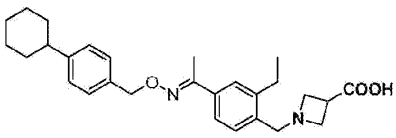
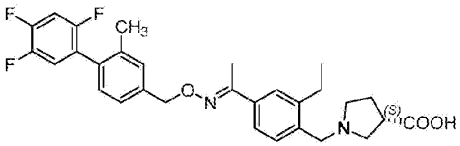
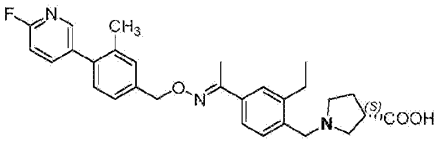
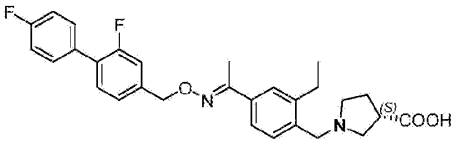


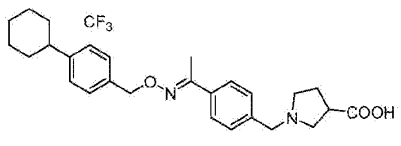
[0029] R^3选自下组的取代基：氢、氰基、卤素、取代或未取代的C_1−C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3−C_8环烷基、氰基、取代或未取代的C_1−C_5烷氧基、取代或未取代的C_1−C_{10}烷基甲酰基、取代或未取代的C_5−C_8芳基甲酰基、取代或未取代的C_5−C_8芳基、取代或未取代的含有1−2个选自N、O或S的杂原子的五元或六元杂环基；

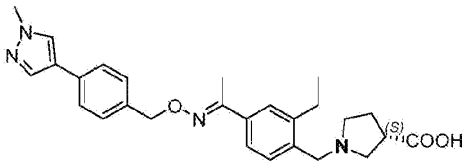
[0030] R^5选自下组：氢、氰基、卤素、取代或未取代的C_1-C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3-C_8环烷基、氰基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的C_5-C_8芳基甲酰基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基；

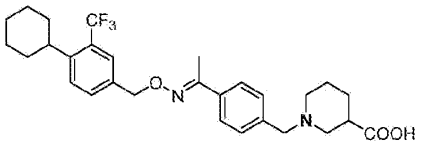
[0031] R^4选自下组：氢、卤素、取代或未取代的C_1-C_{10}烷基、取代或未取代的C_3-C_8环烷基或环烯基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的芳基甲酰基。

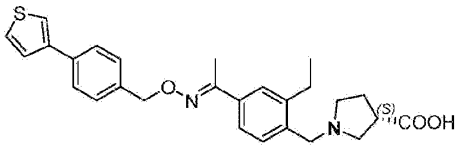
[0032] 在具体的实施方式中，本发明提供选自下组的化合物、或其旋光异构体或药学上可接受的盐：

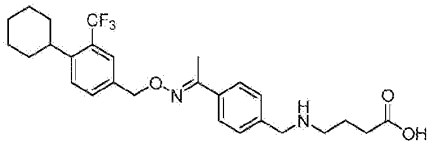









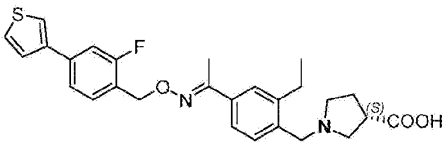


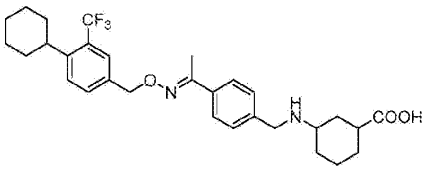


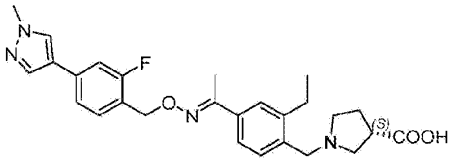


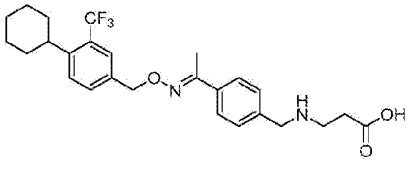


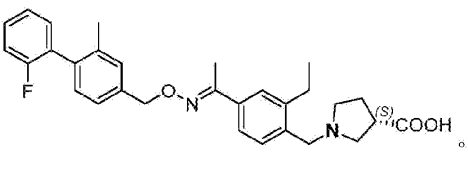


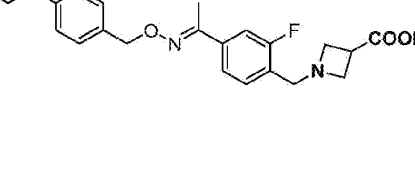


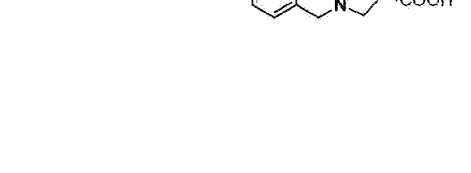


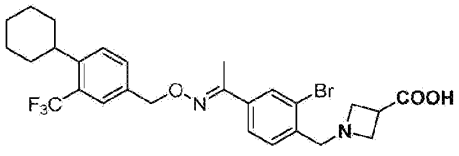


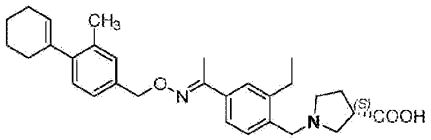


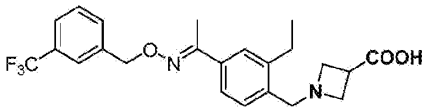


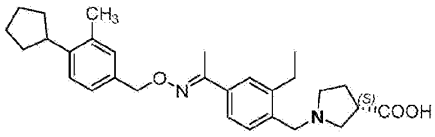


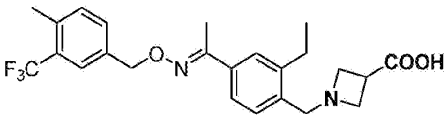


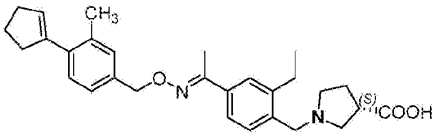


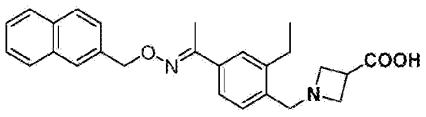


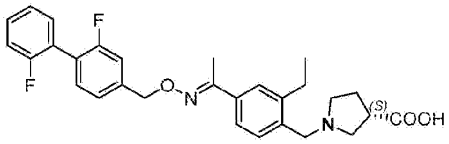


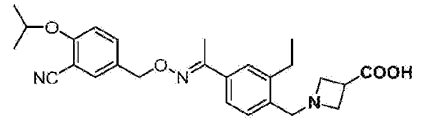


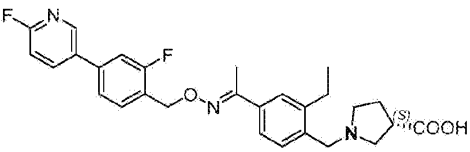


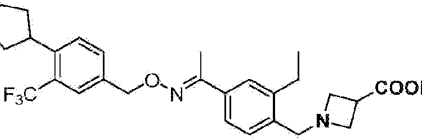


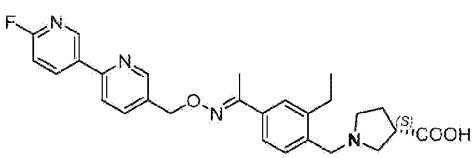


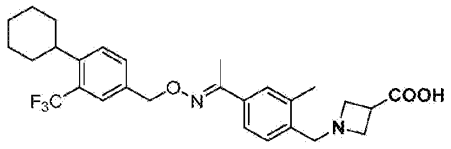


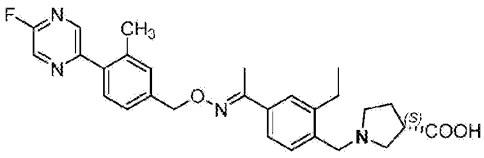


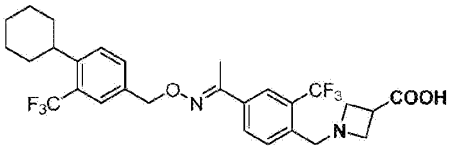


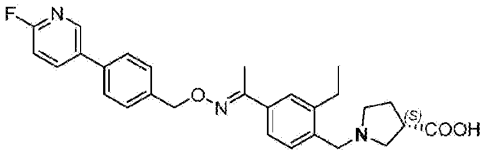


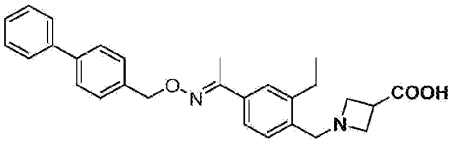


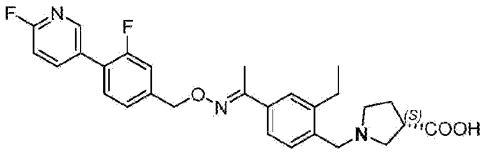


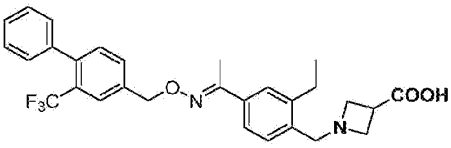


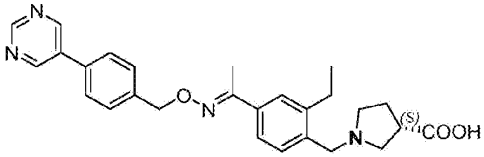


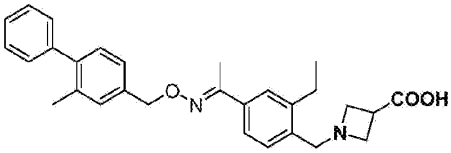


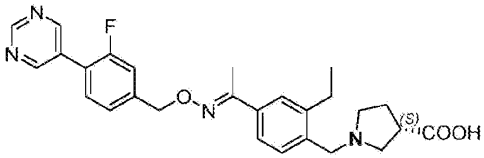


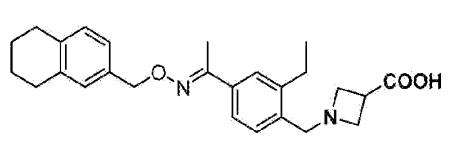


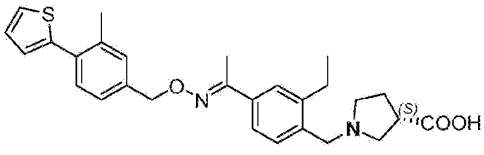


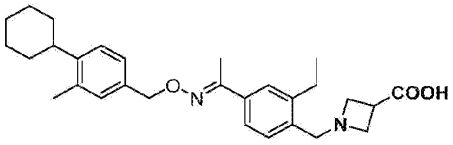


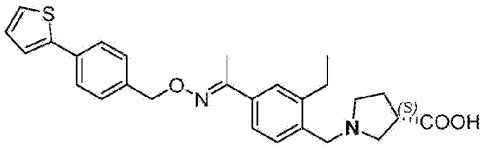


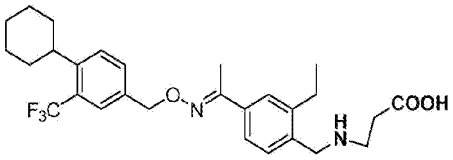


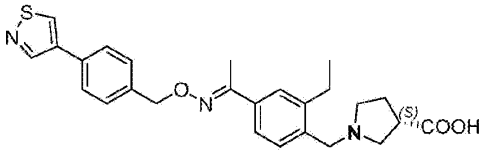


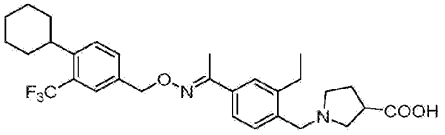


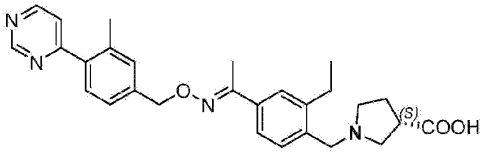


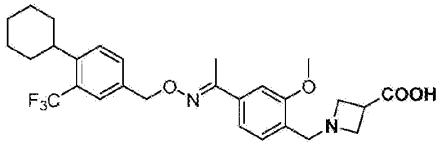


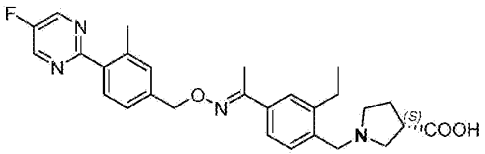


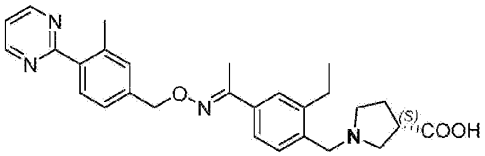


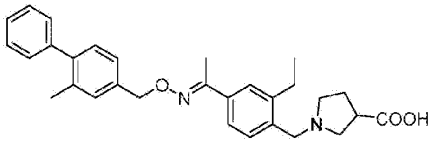


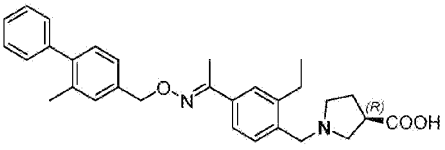


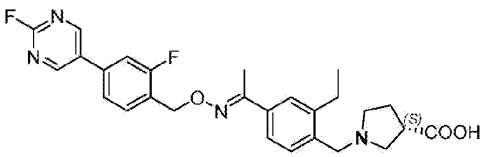


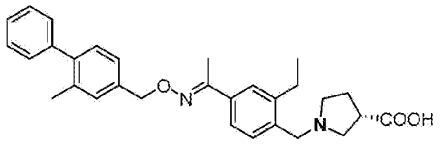


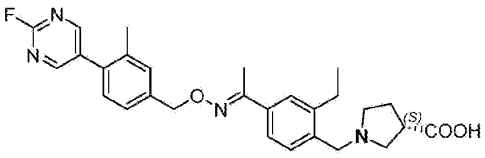


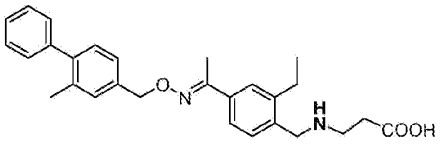


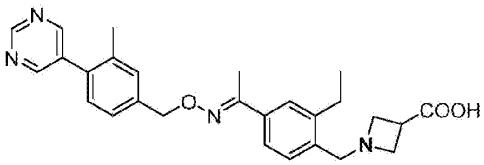


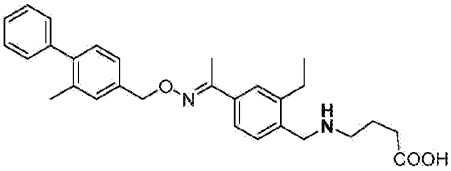


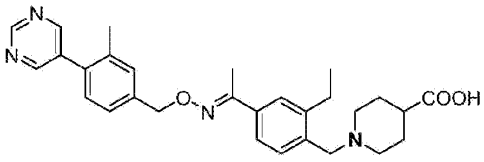


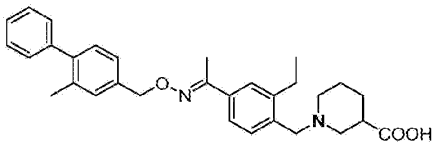


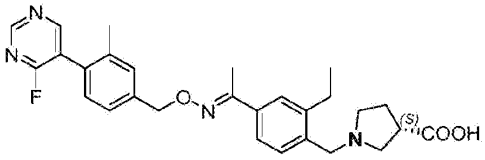


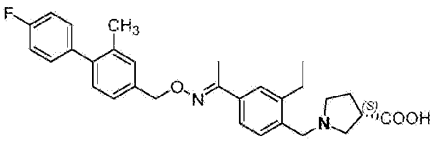


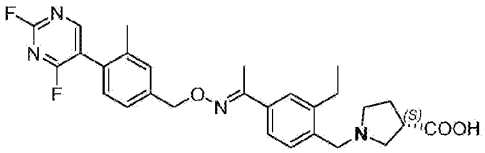


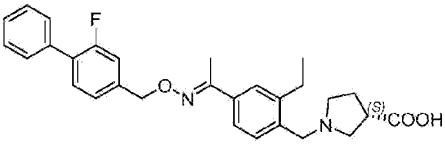


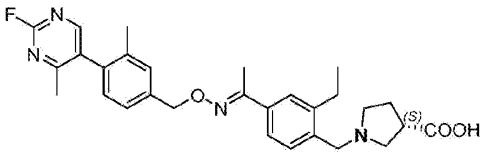


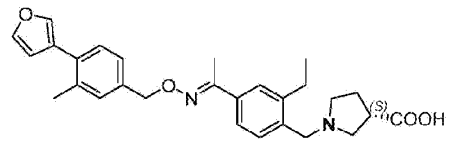
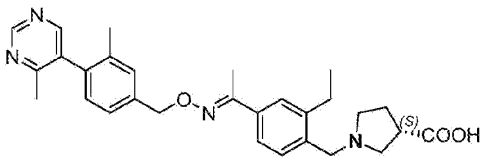
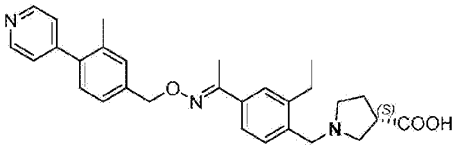
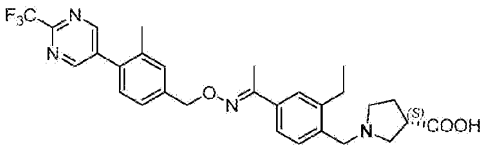
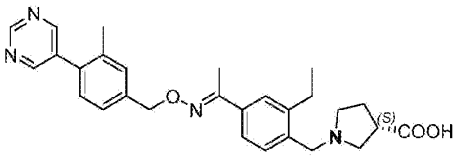
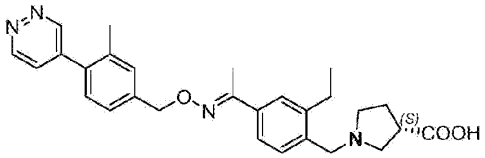
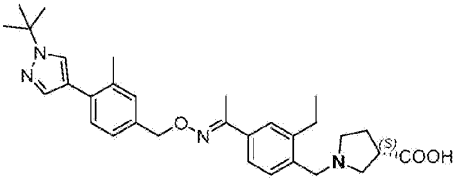
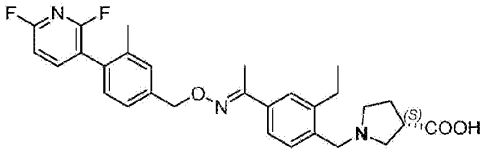
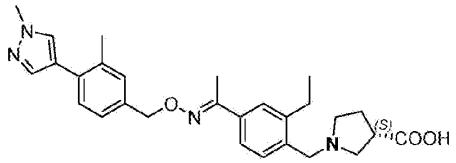
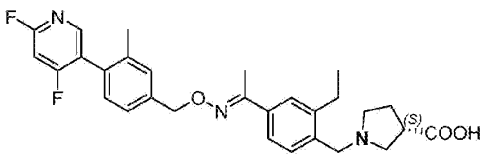


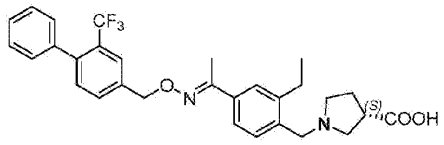


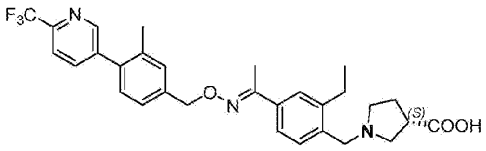


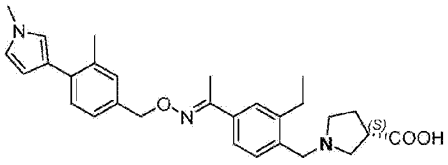


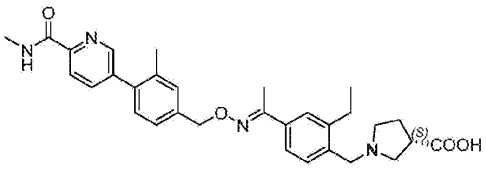


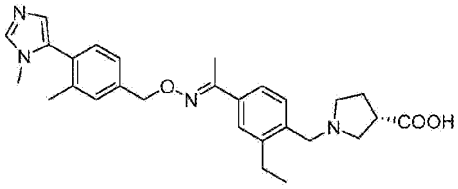











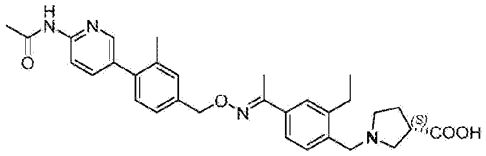


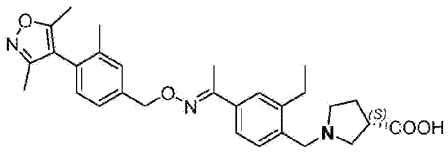


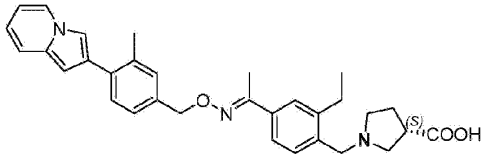


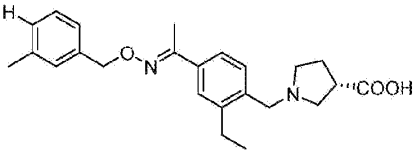


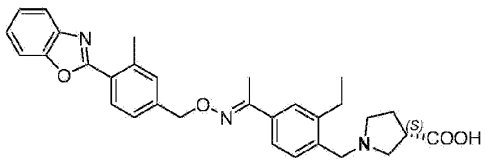


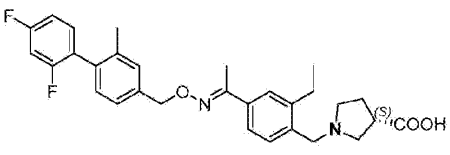


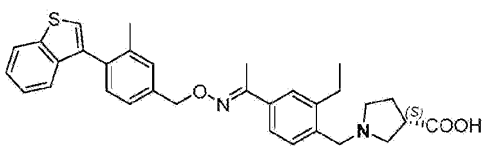


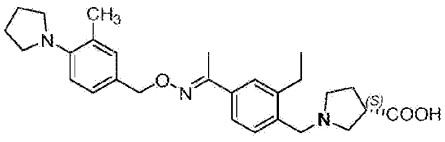


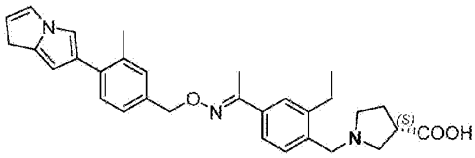


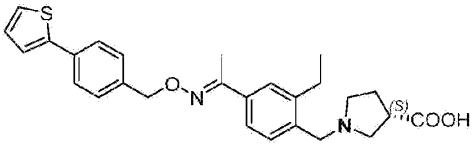


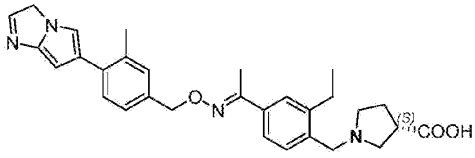


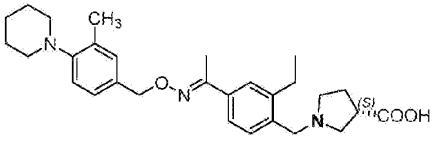


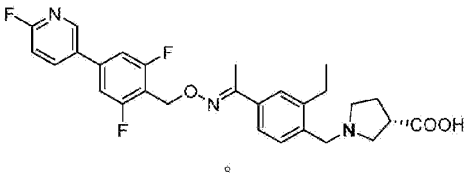


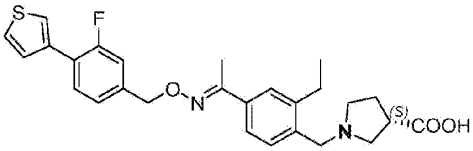


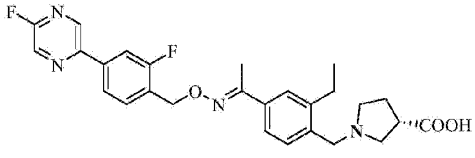


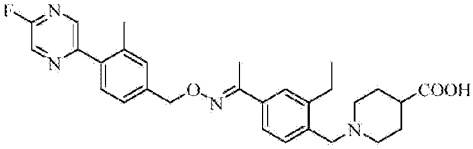


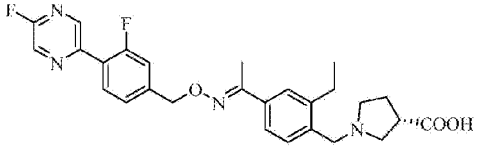


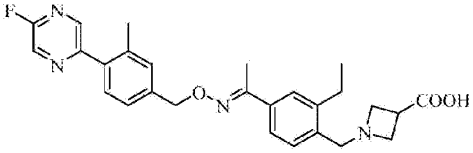


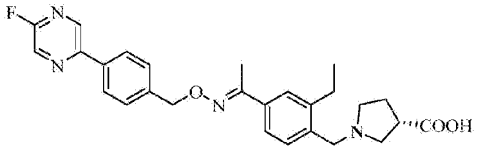


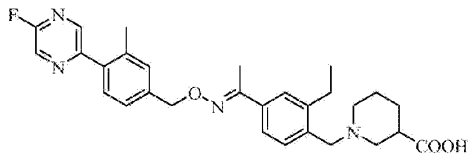
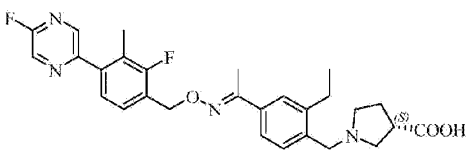
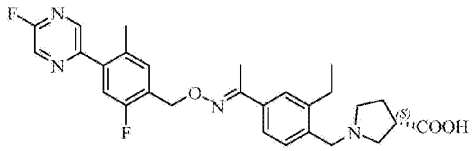
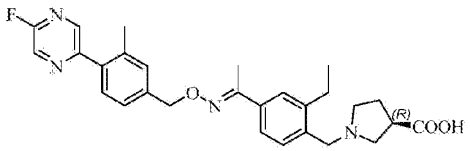
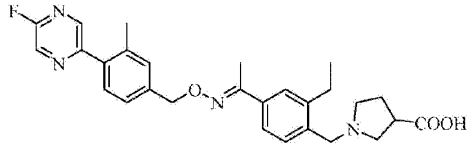
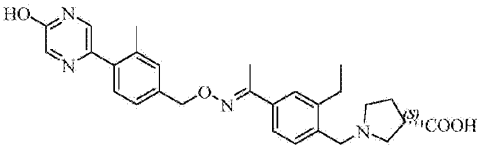






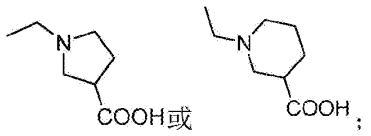




[0033] 在具体的实施方式中，式Ⅲ中，R^1选自下组：氢、卤素(优选F、Cl或Br)、氰基、取代或未取代的C_1-C_5烷氧基(优选甲氧基)、取代或未取代的C_1-C_6烷基(优选甲基、乙基、丙基)；

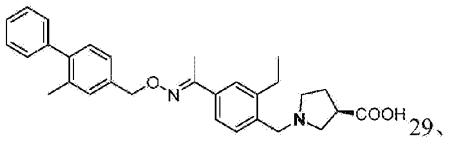
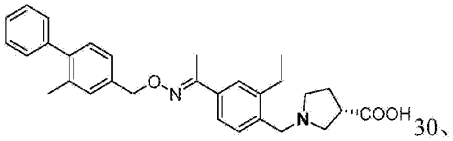
[0034] R^2为：

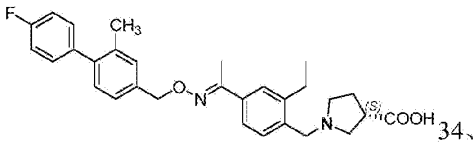


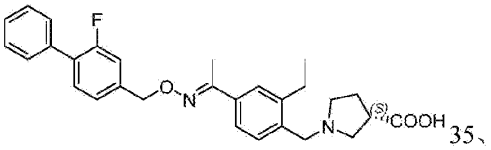
[0035] R^3和R^5独立选自下组：氢、取代或未取代的C_1-C_6烷基(优选甲基、乙基或丙基)、卤素(优选F)；

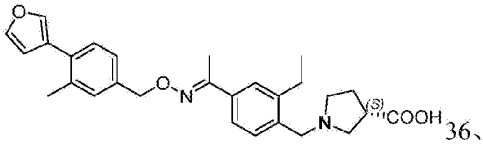
[0036] R^4选自下组：取代或未取代的C_5-C_8芳基(优选苯基或F取代的苯基)、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基。

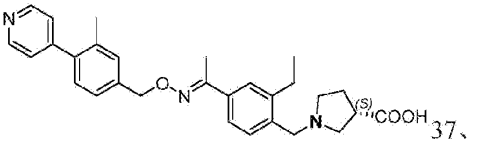
[0037] 在具体的实施方式中，本发明提供选自下组的化合物、或其旋光异构体或药学上可接受的盐：

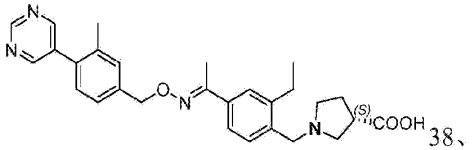

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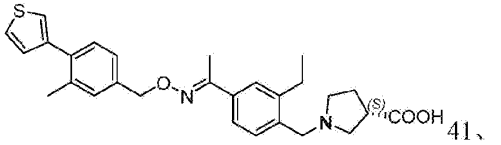

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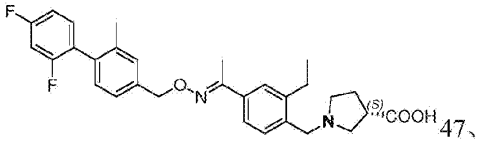

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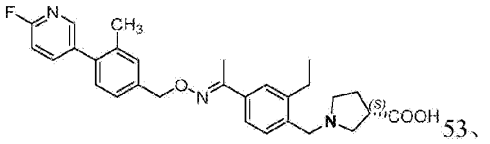

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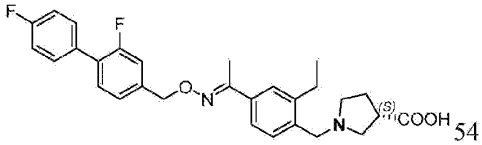

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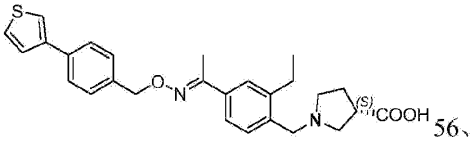

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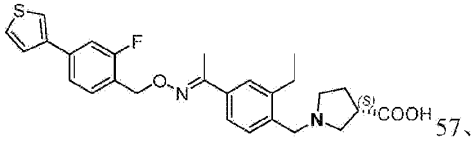

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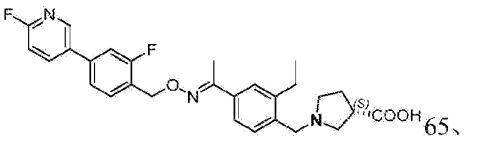

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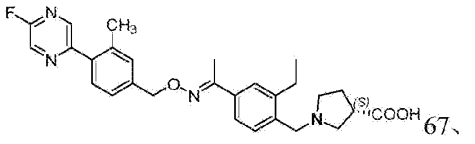

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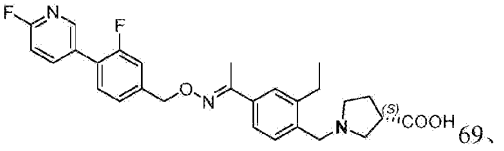

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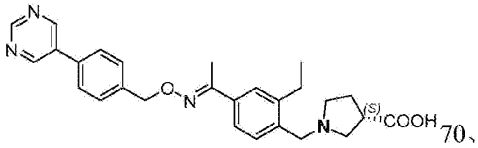

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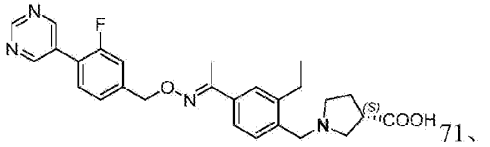

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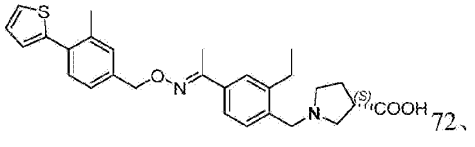

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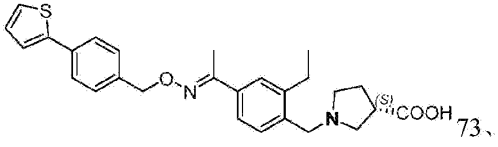

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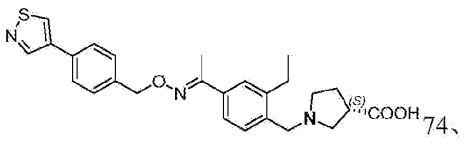

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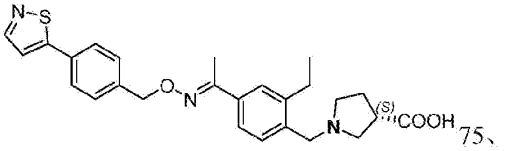

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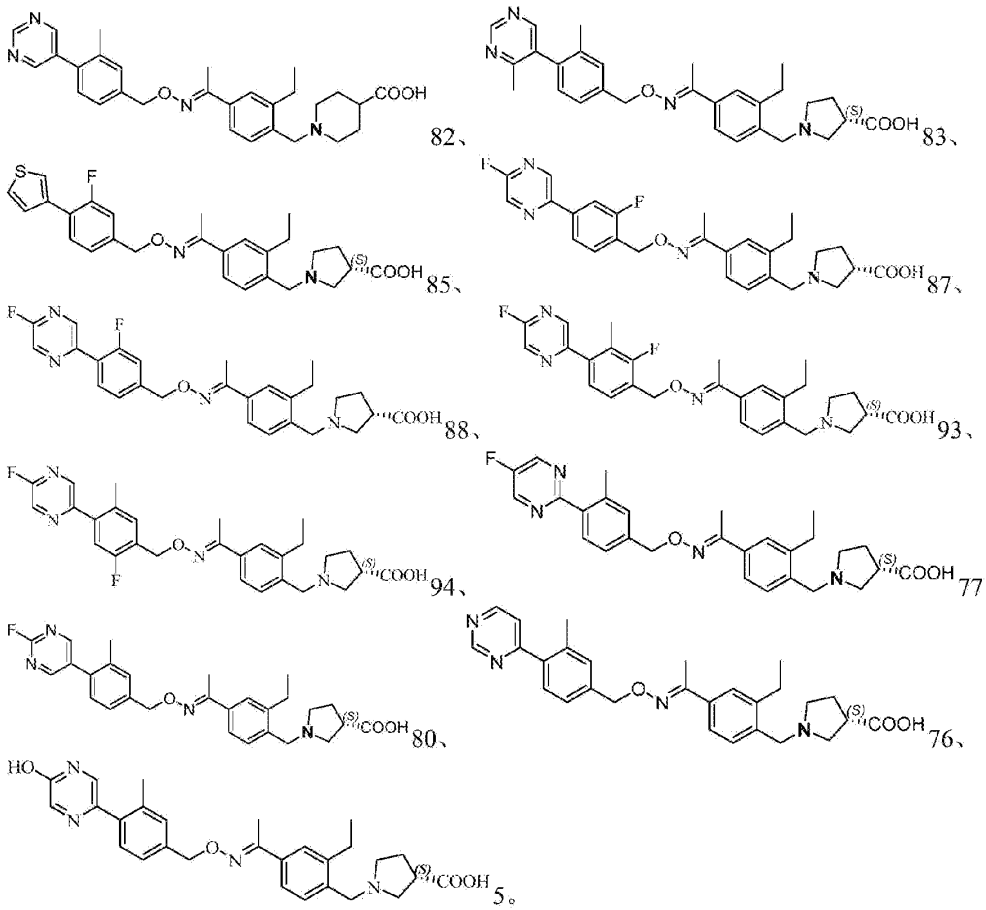

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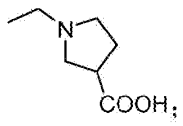

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[0038] 在具体的实施方式中，式Ⅲ中，R^1选自下组：氰基、取代或未取代的C_1-C_5烷氧基(优选甲氧基)、取代或未取代的C_1-C_6烷基(优选甲基、乙基、丙基)；

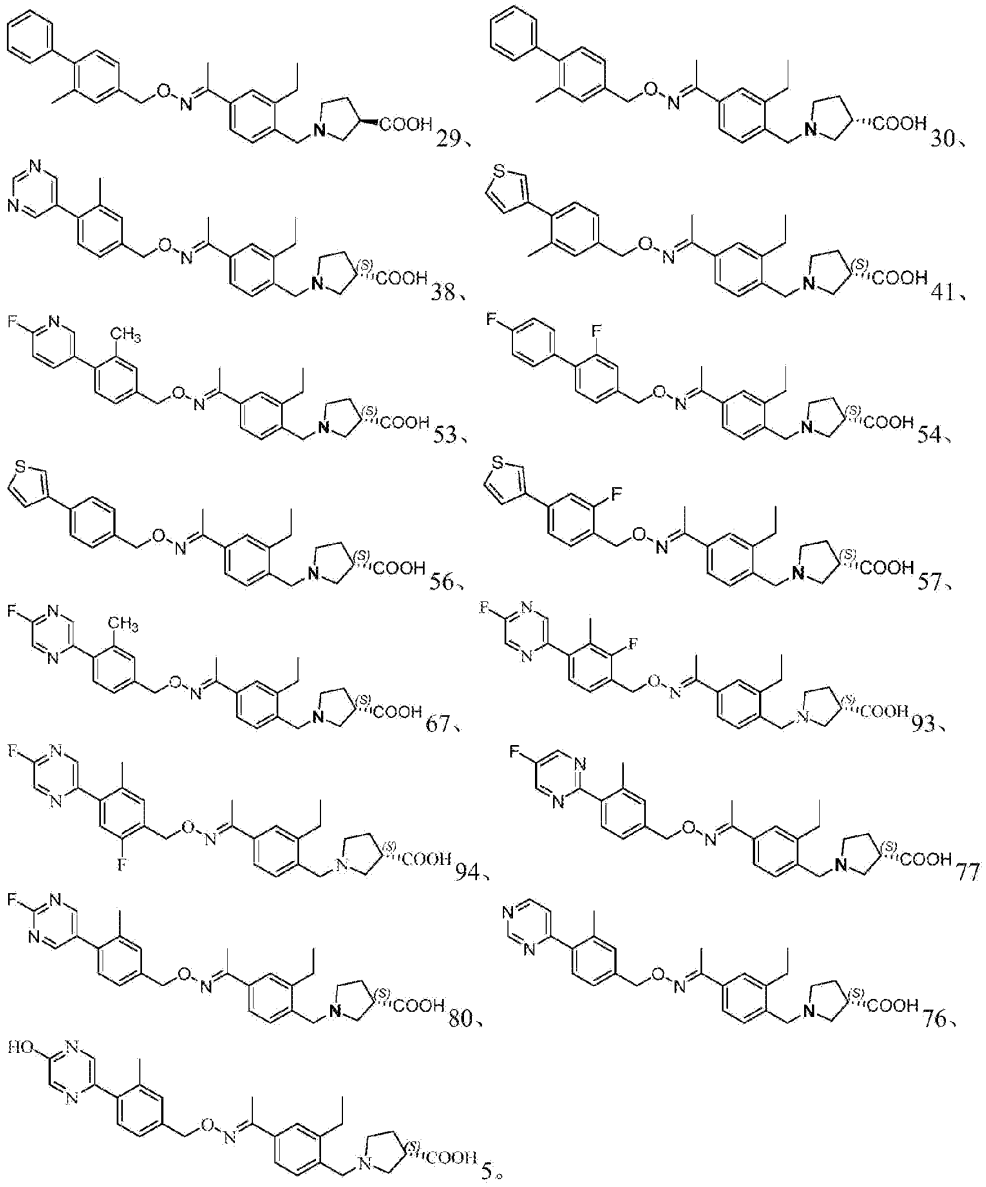
[0039] R^2为：



[0040] R^3和R^5独立选自下组：氢、取代或未取代的C_1-C_3烷基(优选甲基、乙基或丙基)、卤素(优选F)；

[0041] R^4选自下组：取代或未取代的C_5-C_8芳基(优选苯基或F取代的苯基)、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂芳基。

[0042] 在具体的实施方式中，本发明提供选自下组的化合物、或其旋光异构体或药学上可接受的盐：



[0043] 在优选的实施方式中，所述化合物是S1PR调节剂；优选地，所述化合物是S1PR4激动剂；更优选地，所述化合物对S1PR4具有激动作用，而对S1PR1不具有激动作用。

[0044] 在第二方面，本发明提供一种药物组合物，所述药物组合物含有第一方面所述的化合物、或其旋光异构体或药学上可接受的盐，以及药学上可接受的载体或赋形剂。

[0045] 在优选的实施方式中，所述药物组合物是适于口服的剂型，包括但不限于片剂、溶液剂、混悬液、胶囊剂、颗粒剂、粉剂。

[0046] 在优选的实施方式中，所述药物组合物用作S1PR4激动剂、S1PR4突变体激动剂。

[0047] 在优选的实施方式中，所述药物组合物用于治疗或预防S1PR4介导的疾病。

[0048] 在优选的实施方式中，所述S1PR4介导的疾病包括自身免疫性疾病。

[0049] 在优选的实施方式中，所述自身免疫性疾病包括但不限于：系统性红斑狼疮、溃疡性结肠炎、克罗恩病、多发性硬化症、类风湿性关节炎、银屑病、强直性脊柱炎等。

[0050] 在第三方面，本发明提供第一方面所述的化合物、或其旋光异构体或药学上可接受的盐在制备S1PR调节剂中的用途，在优选的实施方式中，所述S1PR调节剂是S1PR4选择性激动剂、S1PR4突变体选择性激动剂。

[0051] 在优选的实施方式中，所述S1PR调节剂是S1PR4激动剂、S1PR4突变体激动剂。

[0052] 在优选的实施方式中，所述S1PR4激动剂、S1PR4突变体激动剂是治疗或预防S1PR4介导的疾病的药物。

[0053] 在优选的实施方式中，所述S1PR4介导的疾病包括自身免疫性疾病。

[0054] 在优选的实施方式中，所述自身免疫性疾病包括但不限于：系统性红斑狼疮、溃疡性结肠炎、克罗恩病、多发性硬化症、类风湿性关节炎、银屑病、强直性脊柱炎等。

[0055] 在第四方面，本发明提供一种在受试者体内调节S1PR的方法，所述方法包括将有效量的第一方面所述的化合物、或其旋光异构体或药学上可接受的盐或第二方面所述的药物组合物给予有此需要的受试者的步骤。

[0056] 在优选的实施方式中，所述方法是在受试者体内激动S1PR4的方法；更优选地，所述方法是在受试者体内激动S1PR4，而不激动S1PR1的方法。

[0057] 在优选的实施方式中，所述方法用于治疗或预防S1PR4介导的疾病。

[0058] 在优选的实施方式中，所述S1PR4介导的疾病包括自身免疫性疾病。

[0059] 在优选的实施方式中，所述自身免疫性疾病包括但不限于：系统性红斑狼疮、溃疡性结肠炎、克罗恩病、多发性硬化症、类风湿性关节炎、银屑病、强直性脊柱炎等。

[0060] 在第五方面，本发明提供第一方面所述的化合物、或其旋光异构体或药学上可接受的盐或权利要求9所述的药物组合物，用于治疗或预防S1PR4介导的疾病。

[0061] 在优选的实施方式中，所述S1PR4介导的疾病包括自身免疫性疾病。

[0062] 在优选的实施方式中，所述自身免疫性疾病包括但不限于：系统性红斑狼疮、溃疡性结肠炎、克罗恩病、多发性硬化症、类风湿性关节炎、银屑病、强直性脊柱炎等。

[0063] 在第六方面，本发明提供一种包含第一方面所述的化合物、或其旋光异构体或药学上可接受的盐或第二方面所述的药物组合物，用于治疗或预防S1PR4介导的疾病的药物。

[0064] 在优选的实施方式中，所述S1PR4介导的疾病包括自身免疫性疾病。

[0065] 在优选的实施方式中，所述自身免疫性疾病包括但不限于：系统性红斑狼疮、溃疡性结肠炎、克罗恩病、多发性硬化症、类风湿性关节炎、银屑病、强直性脊柱炎等。

[0066] 应理解，在本发明范围内中，本发明的上述各技术特征和在下文(如实施例)中具体描述的各技术特征之间都可以互相组合，从而构成新的或优选的技术方案。限于篇幅，在此不再一一累述。

附图说明

[0067] 图1显示了化合物30诱导S1PR4内化后的恢复效果；

[0068] 图2显示了化合物30降低红斑狼疮动物的死亡率；

[0069] 图3显示了化合物30剂量依赖地减少SLE小鼠的皮下结节和抗核抗体水平；

[0070] 图4显示了化合物30调节T淋巴细胞的数量及比值；

[0071] 图5显示了化合物30改善SLE的肾损伤性病理变化；

[0072] 图6显示了给药化合物30的急性UC模型小鼠生存曲线；

[0073] 图7显示了化合物30对急性UC模型小鼠体重影响；

[0074] 图8显示了化合物30对急性UC模型小鼠每日DAI评分影响；

[0075] 图9显示了化合物30对急性UC模型小鼠DAI评分总和影响；

[0076] 图10显示了实验各组结肠长度；

[0077] 图11显示了实验各组结肠重量；

[0078] 图12显示了实验各组结肠肿胀率；

[0079] 图13显示了H&E染色检测小鼠结肠病理变化；

[0080] 图14显示了H&E染色各组小鼠结肠病理评分；

[0081] 图15显示了免疫组化检测急性UC小鼠结肠中的Occludin；

[0082] 图16显示了免疫组化检测急性UC小鼠结肠中的Occludin；

[0083] 图17显示了慢性UC造模期间各组体重变化；

[0084] 图18显示了开始给药后各组体重变化；

[0085] 图19显示了给药前后各组体重变化率；

[0086] 图20显示了造模期间慢性UC模型每日DAI评分；

[0087] 图21显示了给药期间慢性UC模型每日DAI评分；

[0088] 图22显示了给药期间各组慢性UC模型每日DAI评分总和；

[0089] 图23显示了慢性UC各组结肠长度；

[0090] 图24显示了慢性UC各组结肠重量；

[0091] 图25显示了慢性UC各组结肠肿胀率；

[0092] 图26显示了H&E染色检测小鼠结肠病理变化；

[0093] 图27显示了H&E染色各组小鼠结肠病理评分；

[0094] 图28显示了免疫组化检测慢性UC小鼠结肠中的Occludin；

[0095] 图29显示了免疫组化检测慢性UC小鼠结肠中的Occludin；

[0096] 图30显示了化合物30/38/53/67/77/80在小鼠急性UC模型中的药效；

[0097] 图31显示了骨关节炎OA实验流程；

[0098] 图32显示了化合物30的骨关节炎实验中各组疼痛指数统计；

[0099] 图33显示了化合物30的骨关节炎实验中各组五分钟行走距离统计；

[0100] 图34显示了化合物30的骨关节炎实验中各组五分钟直立次数统计；

[0101] 图35显示了化合物30的骨关节炎实验中各组膝关节解剖图；

[0102] 图36显示了化合物30的骨关节炎实验中大鼠膝关节番红固绿染色及OARSI评分的影响；

[0103] 图37显示了化合物67的骨关节炎实验中疼痛指数统计；

[0104] 图38显示了化合物67的骨关节炎实验中各组五分钟行走距离统计；

[0105] 图39显示了化合物67的骨关节炎实验中各组五分钟直立次数统计；

[0106] 图40显示了化合物67的骨关节炎实验中各组膝关节解剖图；

[0107] 图41显示了化合物67的骨关节炎实验中大鼠血清细胞因子的影响；

[0108] 图42显示了化合物67的骨关节炎实验中大鼠膝关节番红固绿染色及OARSI评分的影响；

[0109] 图43显示了化合物67的系统性红斑狼疮实验中8周内红斑狼疮MRL/Lpr模型小鼠的体重和存活率情况；

[0110] 图44显示了化合物67的系统性红斑狼疮实验中化合物67明显降低小鼠尿微量白蛋白水平；

[0111] 图45显示了化合物67的系统性红斑狼疮实验中化合物67明显降低小鼠抗双链DNA抗体水平；

[0112] 图46显示了化合物67的系统性红斑狼疮实验中化合物67明显降低小鼠血肌酐水平；

[0113] 图47显示了化合物67的系统性红斑狼疮实验中化合物67调节T淋巴细胞的数量及比值；

[0114] 图48显示了化合物67的系统性红斑狼疮实验中；

[0115] 图49显示了小鼠强直性脊柱炎模型中各组小鼠外周临床症状评分(8周)；

[0116] 图50显示了小鼠强直性脊柱炎模型中各组小鼠外周临床症状评分(12周)；

[0117] 图51显示了小鼠强直性脊柱炎模型中各组小鼠足部炎症症状典型照片；

[0118] 图52显示了小鼠强直性脊柱炎模型中各组小鼠脊柱CT影像学评分；

[0119] 图53显示了小鼠强直性脊柱炎模型中各组小鼠脊柱CT典型照片；和

[0120] 图54显示了IMQ造模后各组皮肤反应情况。

具体实施方式

[0121] 发明人经过广泛而深入的研究，发现S1PR4激动剂在动物水平对某些自身免疫疾病有治疗效果。进一步地，本发明人合成了具有S1PR4受体调节活性的候选化合物。对得到的候选化合物进行结构优化，设计并合成了一系列未见文献报道的选择性S1PR4化合物，并进行了结构表征。对此系列化合物进行了细胞水平的活性测试，得到一批具备S1PR4激动活性的化合物。这些化合物能够调节S1P受体活性，其中对S1PR4激动活性的EC_{50}值达到nM级别，对S1PR4具有很好的靶向作用。在此基础上完成了本发明。

[0122] 术语定义

[0123] 本文中涉及到的一些基团定义如下：

[0124] 本文中，“烷基”指碳链长度为1-10个碳原子的饱和的支链或直链或环烷基，优选的烷基包括长1-5个、1-2个、1-6个、1-4个、3-8个碳原子不等的烷基。烷基的例子包括但不限于：甲基、乙基、正丙基、异丙基、正丁基、异丁基、庚基等。烷基可以被1个或多个取代基取代，例如被卤素或卤代烷基取代。例如，烷基可以是被1-4个氟原子取代的烷基，或者烷基可以是被氟代烷基取代的烷基。

[0125] 本文中，“链烯基”通常表示具有至少一个双键的单价烃基，通常含有2-8个碳原子，优选含有2-6个碳原子，可以是直链或支链。链烯基的例子包括但不限于乙烯基、丙烯基、异丙烯基、丁烯基、异丁烯基、己烯基等等。

[0126] 本文中，“酯基”通常表示具有至少一个酯基的羧酸衍生物，通常含有3-8个碳原子，优选含有3-6个碳原子，可以是直链或支链。酯基的例子包括但不限于甲酸甲酯、甲酸乙酯、乙酸甲酯、乙酸乙酯、乙酸丙酯等等。

[0127] 本文中，“羟基”指碳链长度为1-10个碳原子的支链或直链醇，通常含有1-10个碳原子，优选含有1-6个碳原子，可以是直链或支链。酯羟基的例子包括但不限于1-羟基正丁基、1-羟基异丁基等等。

[0128] 本文中，“酰氨基”指结构式为“-R’-NH-C(O)-R”的基团，其中，R’可选自氢或烷基，R可选自烷基、链烯基、炔基、被NR_cR_d取代的烷基、被NR_cR_d取代的链烯基和NR_cR_d取代的炔基、被卤素取代的烷基、被氰基取代的链烯基，其中，R_c和R_d可选自烷基和链烯基。

[0129] 本文中，“芳基”指含有6到14个碳原子的单环、双环或三环芳族基团，包括苯基、萘基、菲基、蒽基、茚基、芴基、四氢化萘基、二氢化茚基等。芳基可任选地被1−5个(例如，1、2、3、4或5个)选自以下的取代基取代：卤素、C_{1-4}醛基、C_{1-6}烷基、氰基、硝基、氨基、酰胺基、羟基、羟甲基、卤素取代的烷基(例如三氟甲基)、卤素取代的烷氧基(例如三氟甲氧基)、羧基、C_{1-4}烷氧基、乙氧甲酰基、$N(CH_3)$和C_{1-4}酰基等、杂环基或杂芳基等。

[0130] 本文中，“杂环基”包括但不限于含有1−3个选自O、S或N的杂原子的5元或6元杂环基团，包括但不限于呋喃基、噻吩基、吡咯基、吡咯烷基、吡唑基、咪唑基、三唑基、噁唑基、吡喃基、吡啶基、嘧啶基、吡嗪基、哌啶基、吗啉基等。

[0131] 本文中，“芳杂环基”是指含有5−14个环原子，并且有6个、10个或14个电子在环体系上共用。而且所含环原子是碳原子和从氧、氮、硫中任选的1−3个杂原子。有用的芳杂环基包括哌嗪基、吗啉基、哌啶基、吡咯烷基、噻吩基、呋喃基、吡喃基、吡咯基、咪唑基、吡唑基、吡啶基、包括但不限制于嘧啶基等。芳杂环基可任选地被1−5个(例如，1、2、3、4或5个)选自以下的取代基取代：卤素、C_{1-4}醛基、C_{1-6}直链或支链烷基、氰基、硝基、氨基、羟基、羟甲基、卤素取代的烷基(例如三氟甲基)、卤素取代的烷氧基(例如三氟甲氧基)、羧基、C_{1-4}烷氧基、乙氧甲酰基、$N(CH_3)$和C_{1-4}酰基。

[0132] 本文中，“烷氧基”指被烷基取代的氧基。优选的烷氧基是长1−6个碳原子的烷氧基，更优选为长1−3个碳原子的烷氧基。烷氧基的例子包括但不限于：甲氧基、乙氧基、丙氧基等。烷氧基可以被1个或多个取代基取代，例如被卤素或卤代烷基取代。例如，烷氧基可以是被1−4个氟原子取代的烷基，或者烷基可以是被氟代烷基取代的烷基。

[0133] 本文中，“卤素”指氟、氯、溴或碘。

[0134] 本文中，“任选取代的”指其所修饰的取代基可任选地被1−5个(例如，1、2、3、4或5个)选自以下的取代基取代：卤素、C_{1-4}醛基、C_{1-6}直链或支链烷基、氰基、硝基、氨基、羟基、羟甲基、卤素取代的烷基(例如三氟甲基)、卤素取代

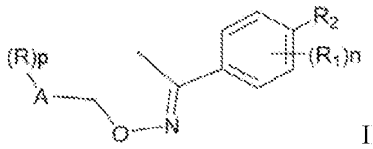
的烷氧基(例如三氟甲氧基)、羧基、C_{1-4}烷氧基、乙氧甲酰基、$N(CH_3)$和C_{1-4}酰基。

[0135] 本发明的化合物

[0136] 本发明人发现一个家系中的男性和女性从50岁开始表现出肌营养不良表型，并且随着年龄的增加而加重，表现出很强的家族遗传性疾病特征。通过对这个家系进行全基因测序等研究，发现NDUFA10和S1PR4突变是肌营养不良疾病的潜在致病基因突变。

[0137] 鉴于目前临床上还没有靶向S1PR4的药物，上市和在研的S1P受体调节剂主要集中在S1PR1和S1PR5相关靶点。本发明人设计并合成了一系列结构全新的在S1PR的不同亚型之间具有选择性的化合物。因此，本发明的化合物对S1PR的不同亚型具有不同的调节作用；换言之，本发明的化合物是S1PR的调节剂。在具体的实施方式中，本发明的化合物是S1PR4激动剂。在优选的实施方式中，本发明的化合物在S1PR4和S1PR1之间具有选择性；即，本发明的化合物对S1PR4具有激动作用，但对S1PR1不具有激动作用。

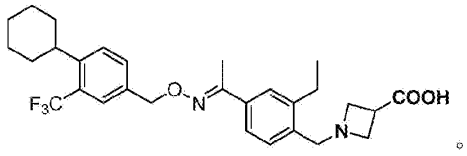
[0138] 在具体的实施方式中，本发明的化合物是下式I所示的化合物，或其光学异构体或药学上可接受的盐，



I

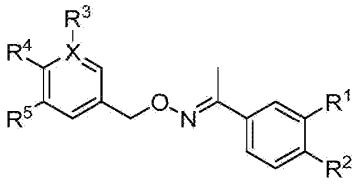
[0139] 式中，A、R、R^1、n、R^2、m、q如上所述。

[0140] 在优选的实施方式中，本发明的化合物不包括以下化合物：



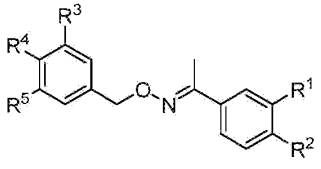
。

[0141] 在优选的实施方式中，本发明的化合物如下式II所示，


II

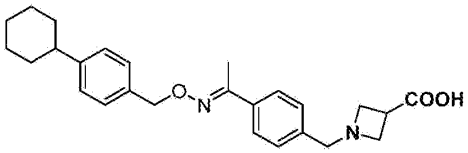
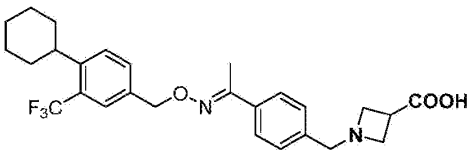
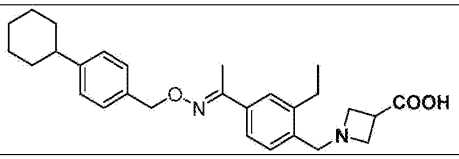
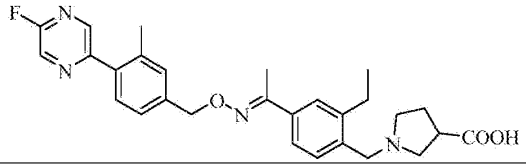
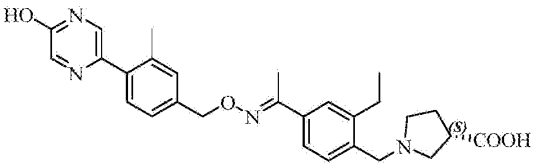
[0142] 式中，R^1、R^2、X、R^3、R^4、R^5如上所述。

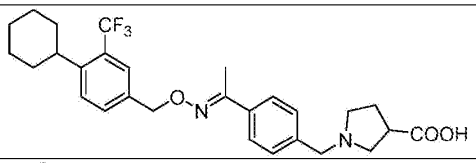
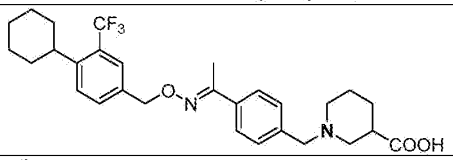
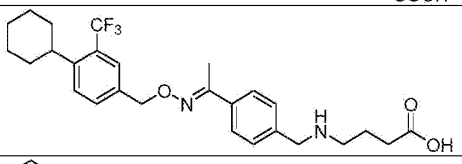
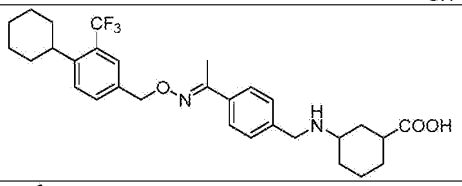
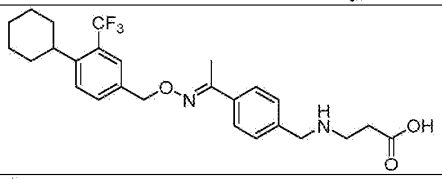
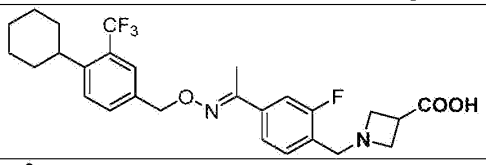
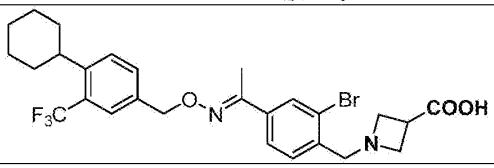
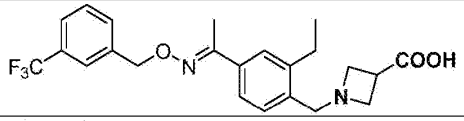
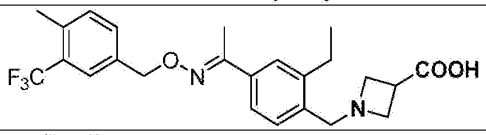
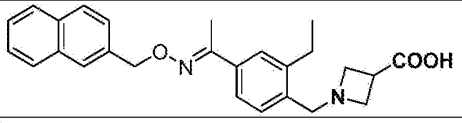
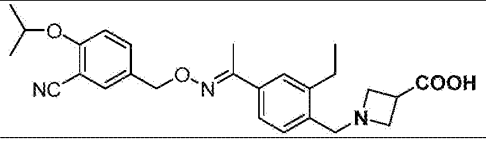
[0143] 在优选的实施方式中，本发明的化合物如下式III所示，

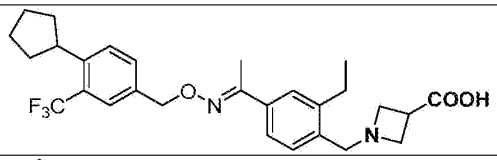
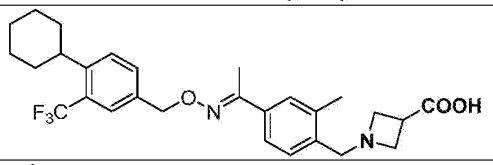
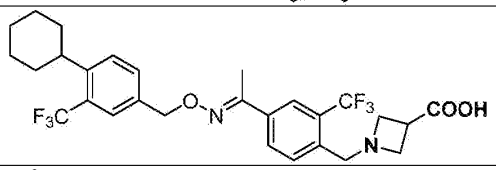
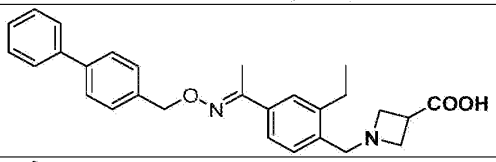
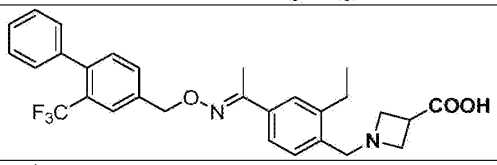
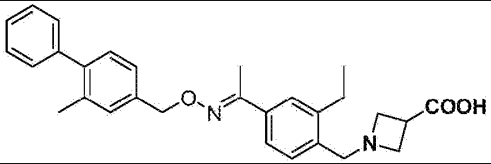
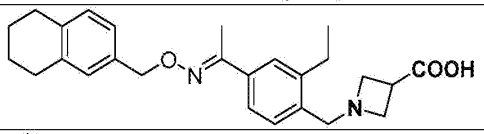
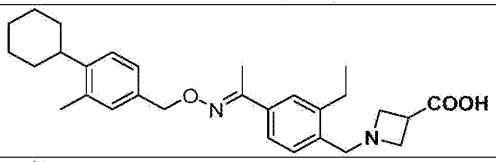
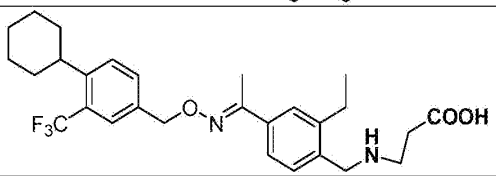
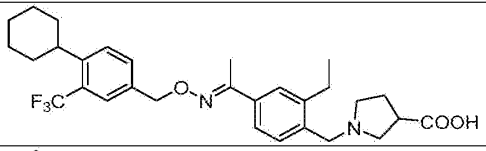
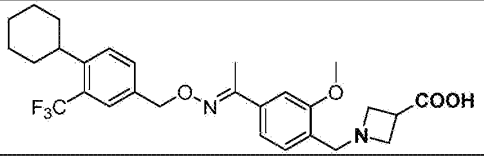

III

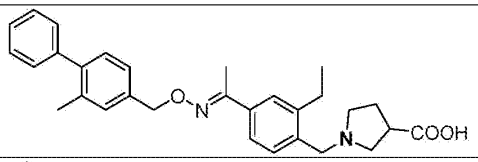
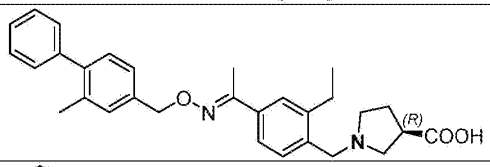
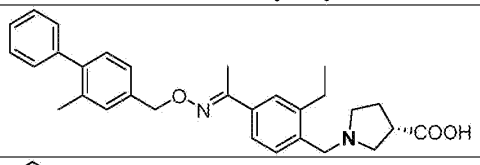
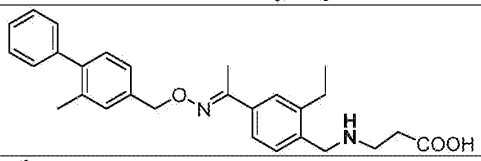
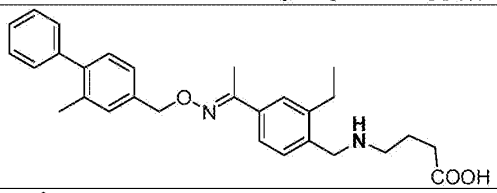
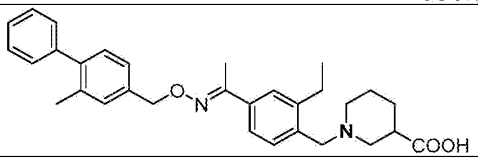
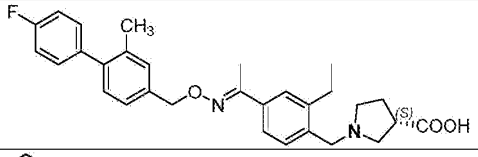
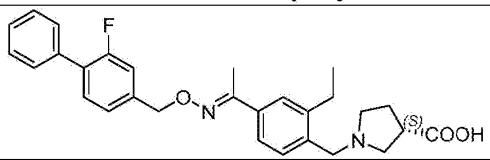
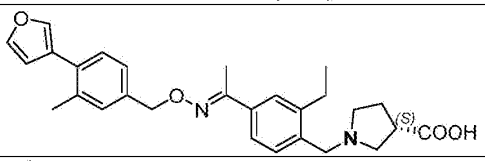
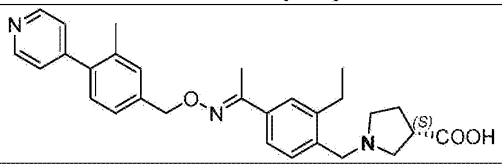
[0144] 式中，R^1、R^2、R^3、R^4、R^5如上所述。

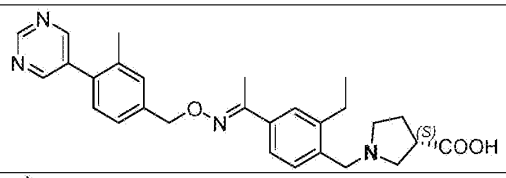
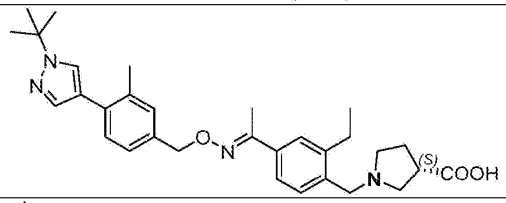
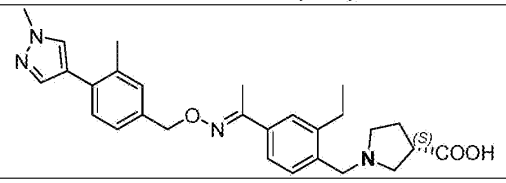
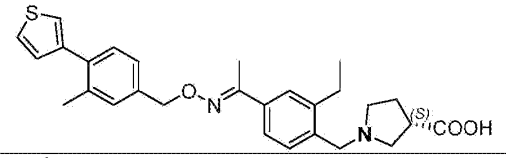
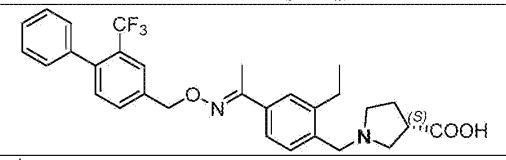
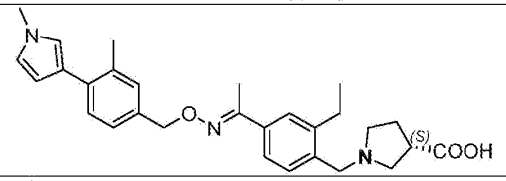
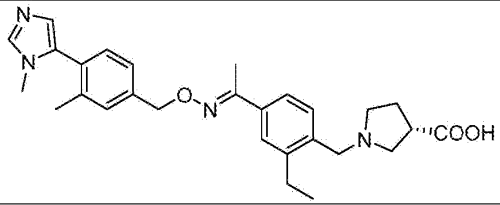
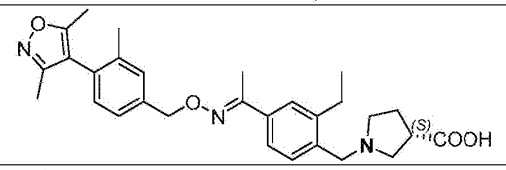
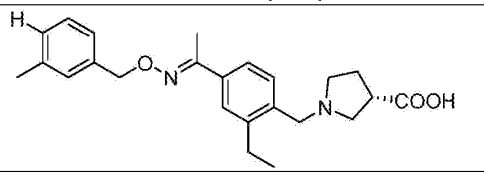
[0145] 具体地说，本发明提供选自下组的化合物、或其旋光异构体或药学上可接受的盐：

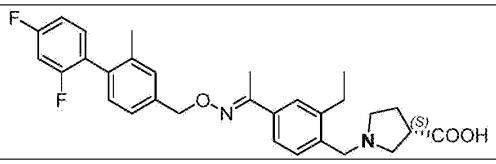
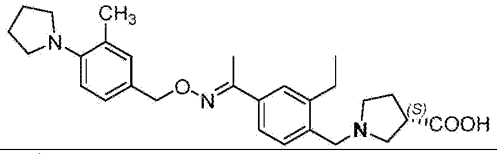
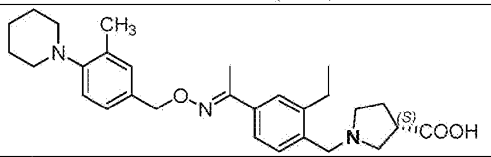
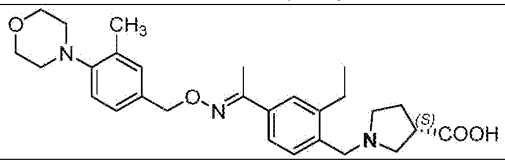
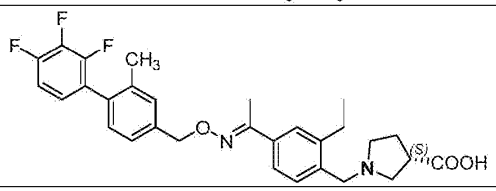
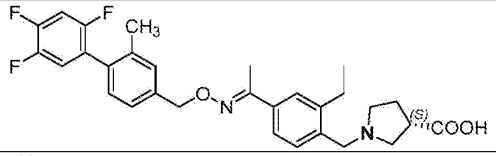
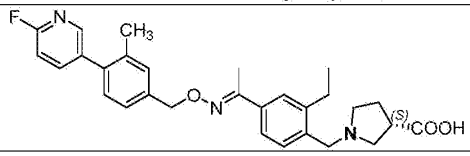
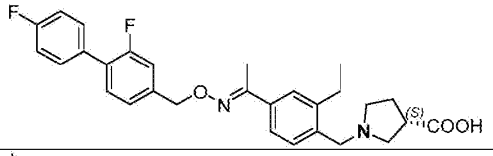
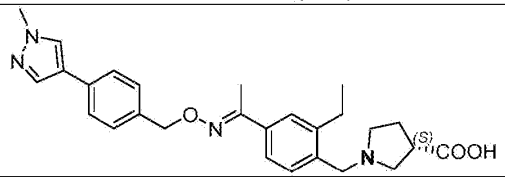
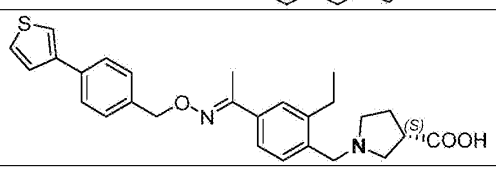
化合物编号	结构式
1	
2	
3	
4	
5	

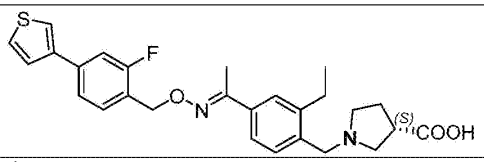
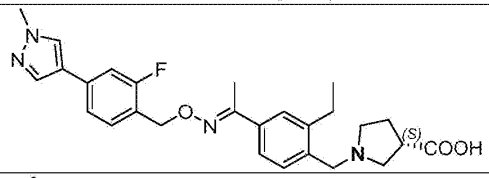
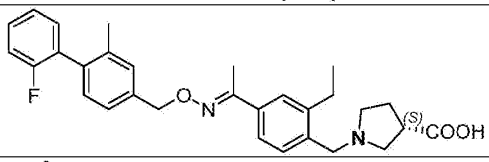
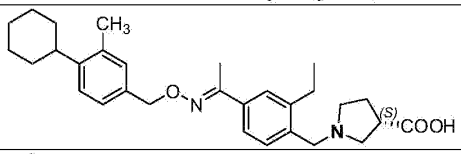
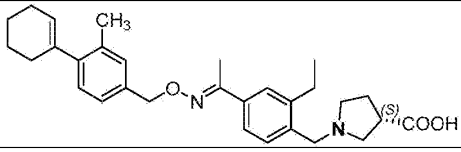
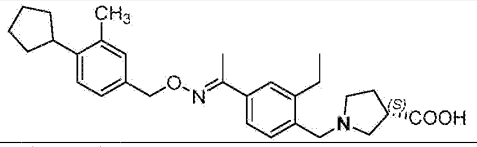
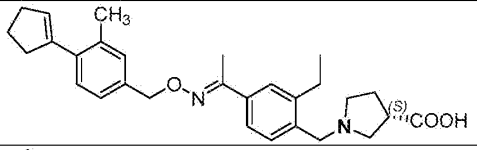
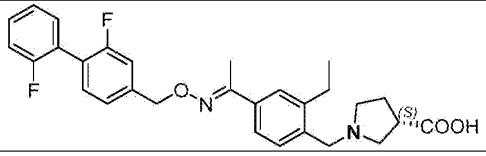
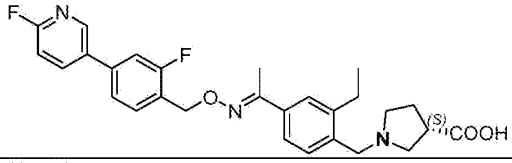
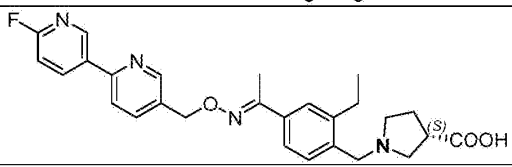
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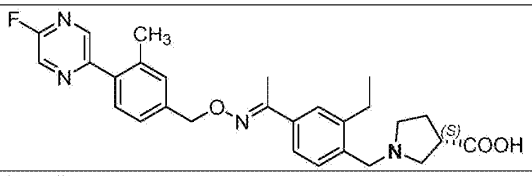
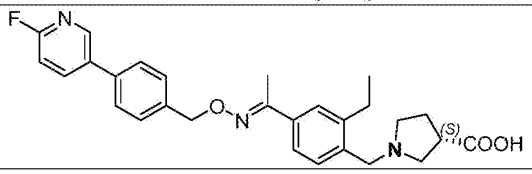
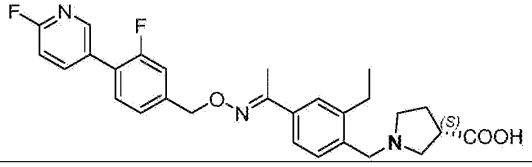
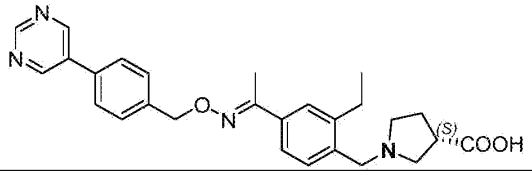
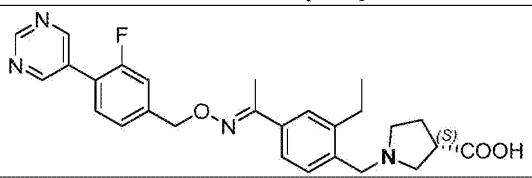
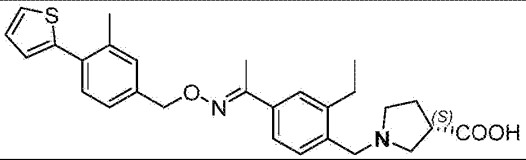
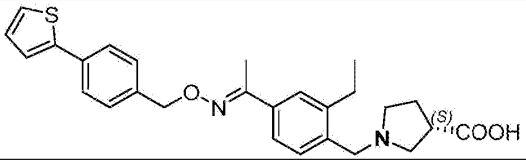
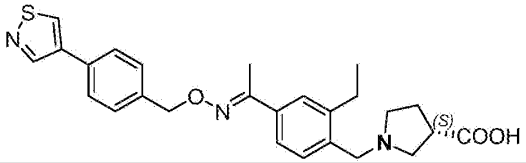
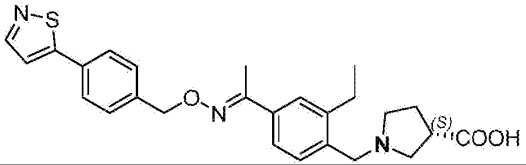
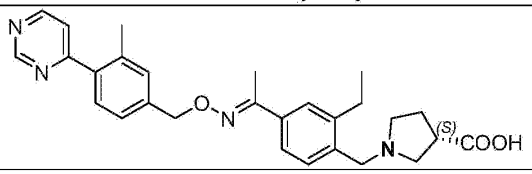
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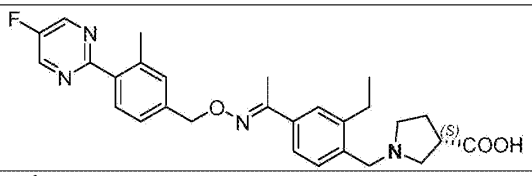
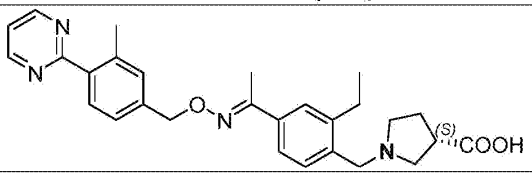
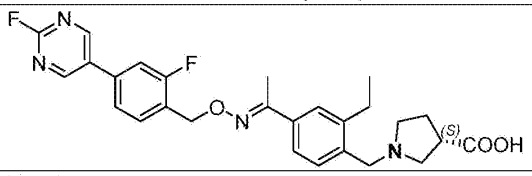
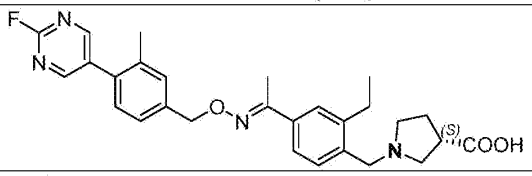
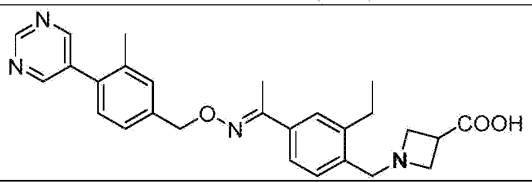
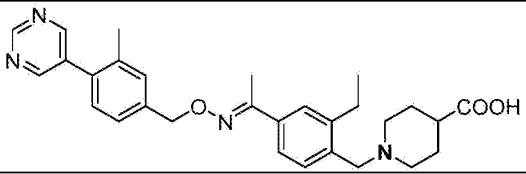
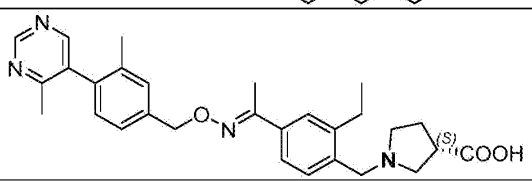
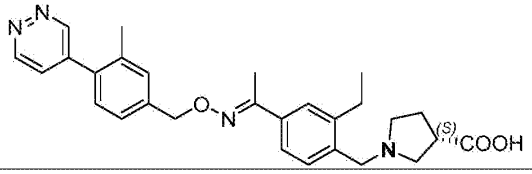
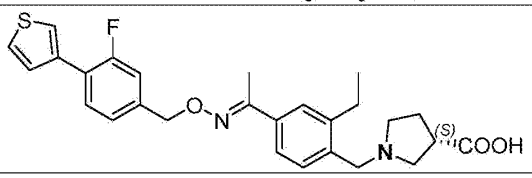
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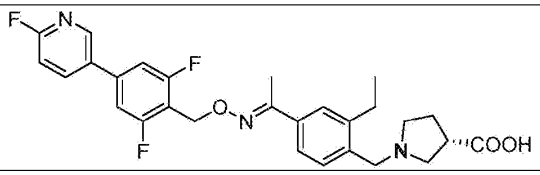
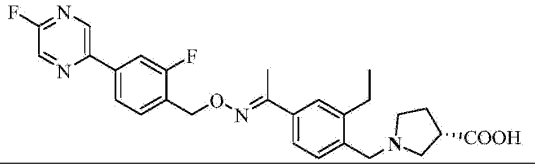
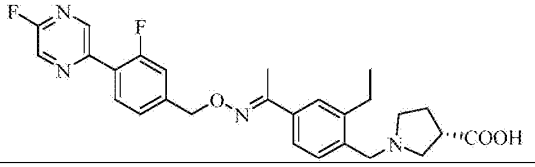
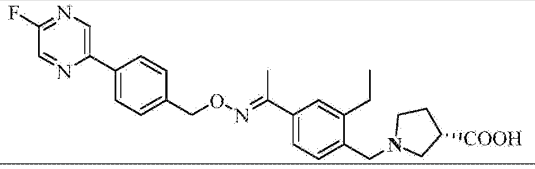
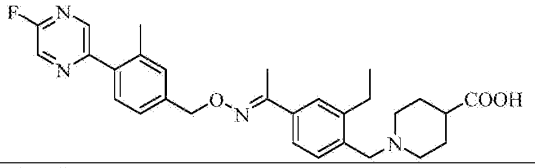
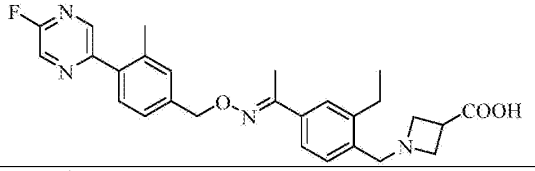
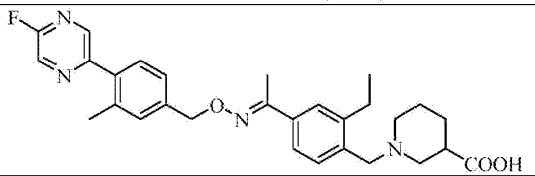
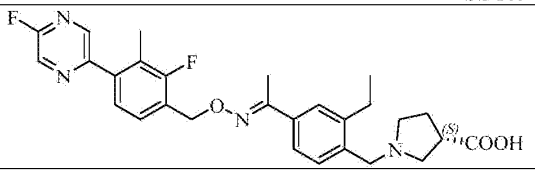
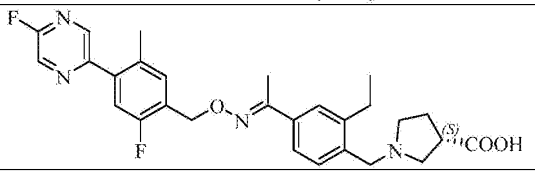
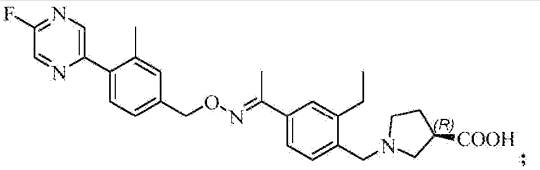
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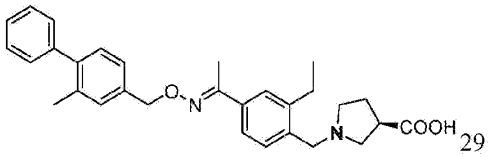
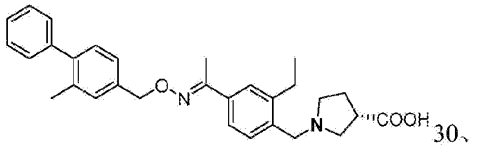
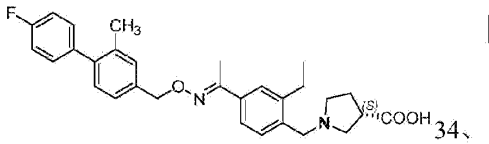
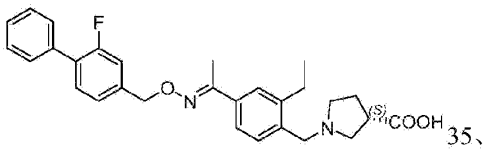
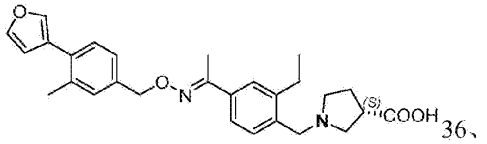
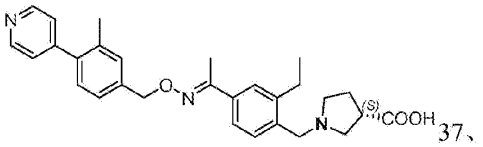
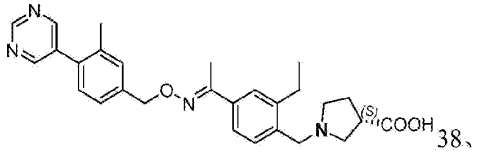
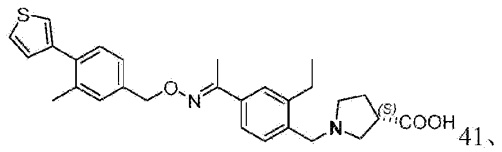
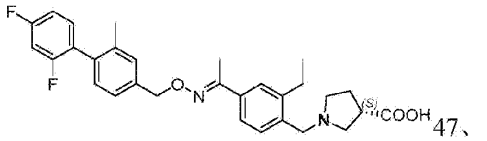
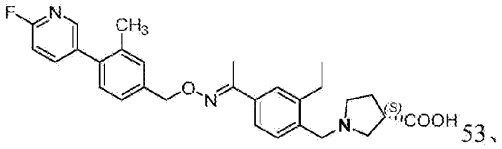
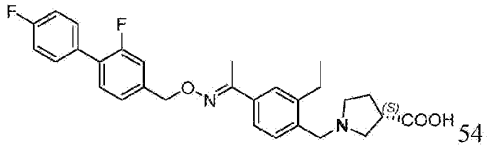
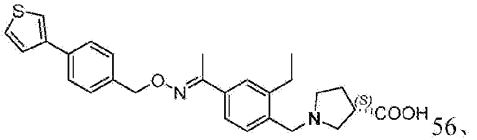
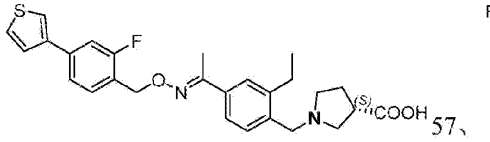
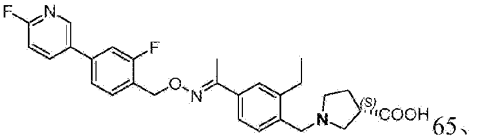
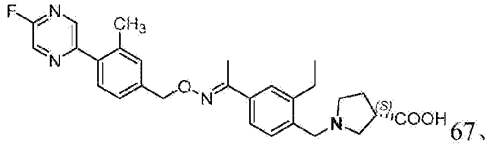
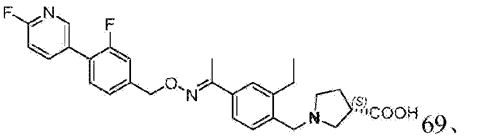
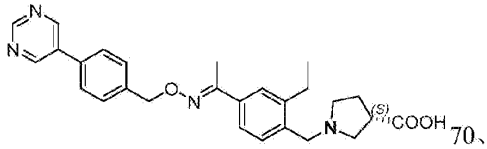
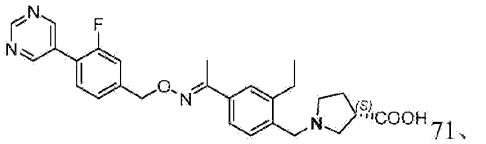
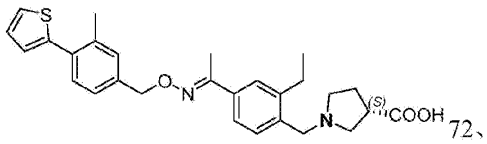
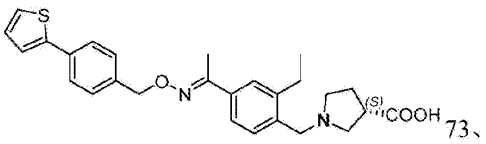
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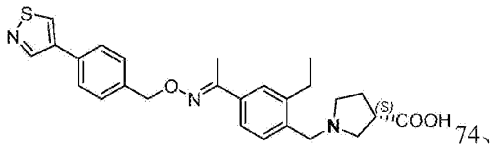
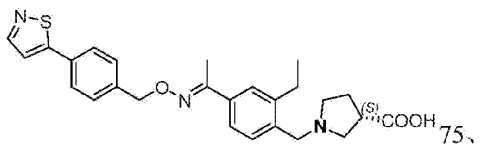
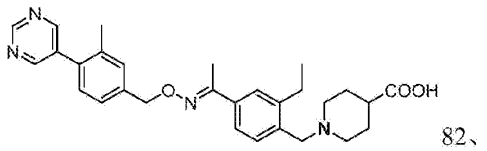
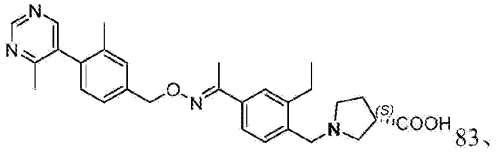
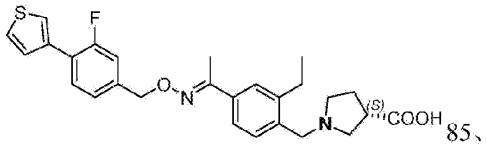
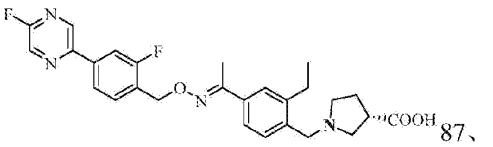
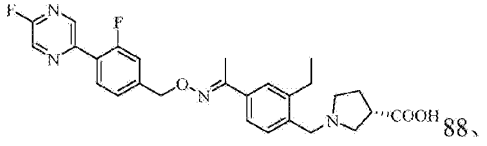
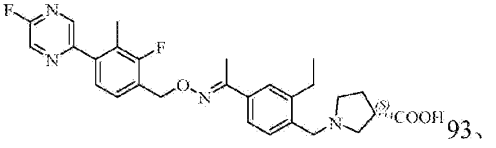
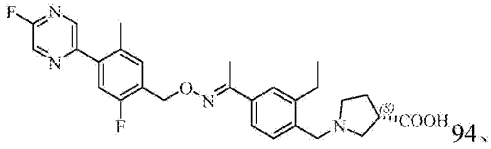
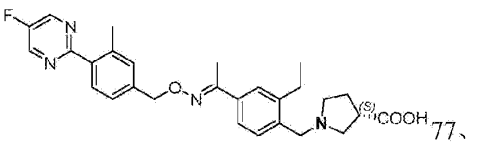
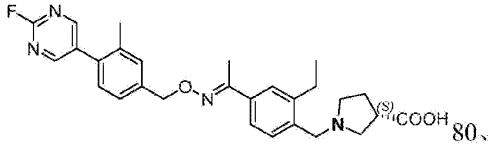
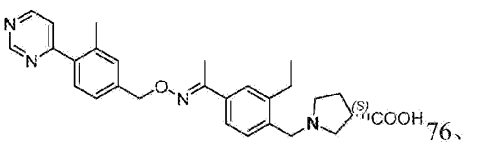
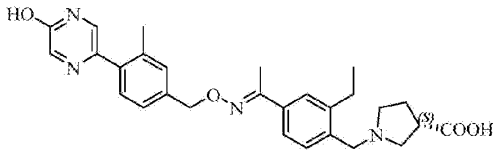
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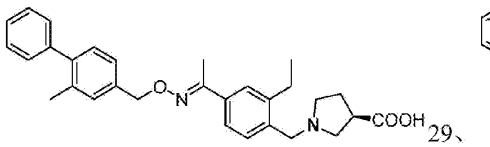
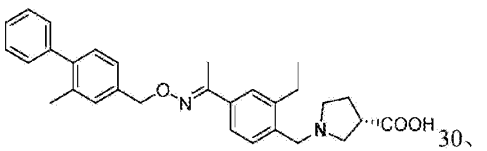
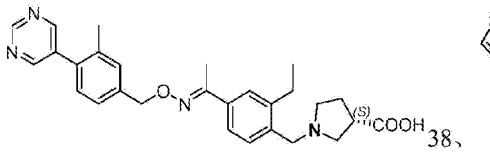
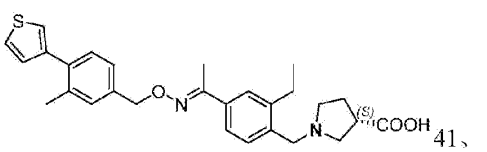
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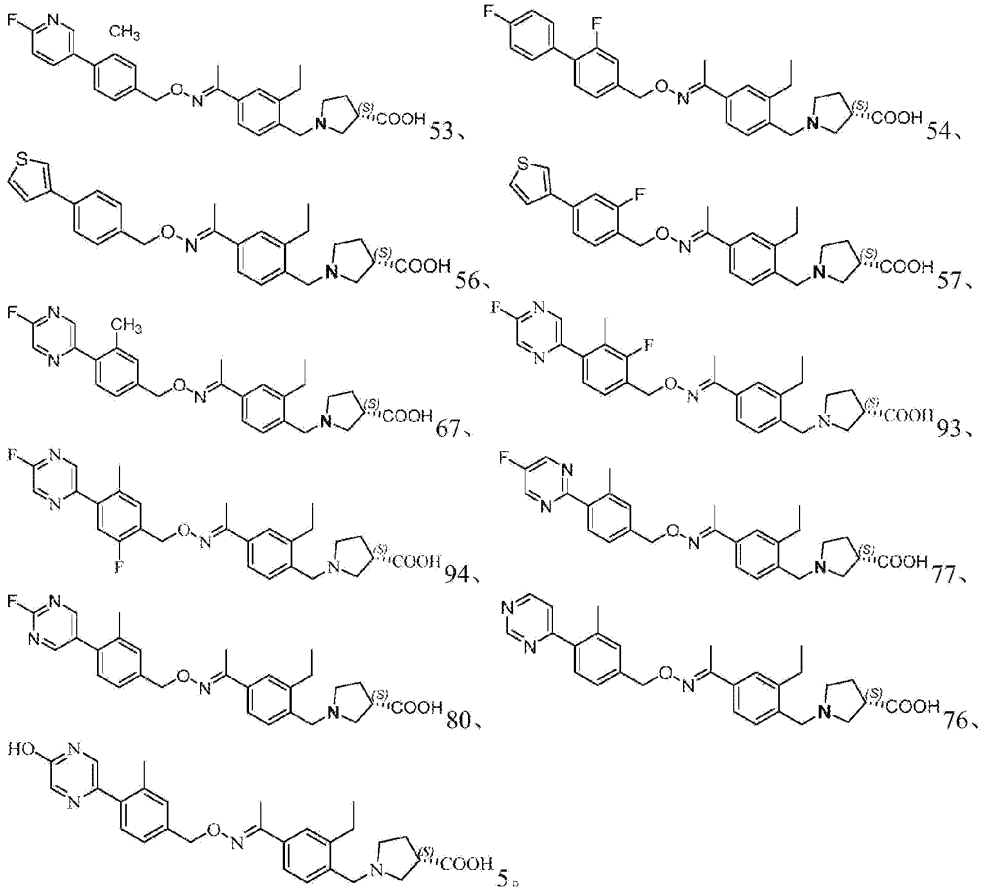
[0146] 优选以下化合物：


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[0147] 更优选以下化合物：


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[0148] 在本发明的化合物的基础上，本发明提供一种药物组合物，该组合物含有治疗有效量的本发明的化合物或其药学上可接受的盐，以及药学上可接受的载体或赋形剂。

[0149] 本发明化合物的药学上可接受的盐的例子包括但不限于无机和有机酸盐，例如盐酸盐、氢溴酸盐、硫酸盐、柠檬酸盐、乳酸盐、酒石酸盐、马来酸盐、富马酸盐、扁桃酸盐和草酸盐；以及与如钠羟基、三(羟基甲基)胺基甲烷(TRIS，胺丁三醇)和N-甲基葡糖胺等碱形成的无机和有机碱盐。

[0150] 本发明的药物组合物可被配制成适合各种给药途径的制剂形式，包括但不限于被配制成用于肠外，皮下，静脉，肌肉，腹腔内，透皮，口腔，鞘内，颅内，鼻腔或外用途径给药的形式，用于治疗肿瘤和其他疾病。给药量是有效地改善或消除一个或多个病症的药量。对于特定疾病的治疗，有效量是足以改善或以某些方式减轻与疾病有关的症状的药量。这样的药量可作为单一剂量施用，或

者可依据有效的治疗方案给药。给药量也许可治愈疾病，但是给药通常是为了改善疾病的症状。一般需要反复给药来实现所需的症状改善。药的剂量将根据病人的年龄，健康与体重，并行治疗的种类，治疗的频率，以及所需治疗效益来决定。

[0151] 本发明的药物制剂可以给予任何哺乳动物，只要他们能获得本发明化合物的治疗效果。在这些哺乳动物中最为重要的是人类。

[0152] 本发明的化合物或其药物组合物可用于制备S1PR调节剂。在具体的实施方式中，所述S1PR调节剂是S1PR4激动剂、S1PR4突变体激动剂。由此，本发明的化合物或其药物组合物可用于治疗各种由S1PR4(包括其突变体)介导的疾病，包括自身免疫疾病。在具体的实施方式中，所述S1PR4(包括其突变体)介导的自身免疫疾病包括但不限于多发性硬化症、类风湿性关节炎、系统性红斑狼疮、银屑病、溃疡性结肠炎、克罗恩病等。

[0153] 本发明的药物制剂可用已知的方式制造。例如，由传统的混合，制粒，制锭，溶解，或冷冻干燥过程制造。制造口服制剂时，可结合固体辅料和活性化合物，选择性研磨混合物。如果需要或必要时加入适量助剂后，加工颗粒混合物，获得片剂或锭剂芯。

[0154] 合适的辅料特别是填料，例如糖类如乳糖或蔗糖，甘露醇或山梨醇；纤维素制剂或钙磷酸盐，例如磷酸三钙或磷酸氢钙；以及粘结剂，例如淀粉糊，包括玉米淀粉，小麦淀粉，大米淀粉，马铃薯淀粉，明胶，黄芪胶，甲基纤维素，羟丙基甲基纤维素，羧甲基纤维素钠，或聚乙烯吡咯烷酮。如果需要，可增加崩解剂，比如上面提到的淀粉，以及羧甲基淀粉，交联聚乙烯吡咯烷酮，琼脂，或褐藻酸或其盐，如海藻酸钠。辅助剂特别是流动调节剂和润滑剂，例如，硅石，滑石，硬脂酸盐类，如镁硬脂酸钙，硬脂酸或聚乙二醇。如果需要，可以給锭剂核芯提供可以抵抗胃液的合适包衣。为此，可以应用浓缩糖类溶液。这个溶液可以含有阿拉伯树胶，滑石，聚乙烯吡咯烷酮，聚乙二醇和/或二氧化钛，漆溶液和合适的有机溶剂或溶剂混合物。为了制备耐胃液的包衣，可使用适当的纤维素溶液，例如醋酸纤维素邻苯二甲酸或羟丙基甲基纤维素邻苯二甲

酸。可向药片或锭剂核芯的包衣加入染料或色素。例如，用于识别或为了表征活性成分剂量的组合。

[0155] 基于上述化合物和药物组合物，本发明进一步提供一种治疗S1PR4介导的疾病的方法，该方法包括给予需要的对象以本发明的化合物或药物组合物。

[0156] 给药方法包括但不限于本领域周知的各种给药方法，可根据患者的实际情况加以确定。这些方法包括但不限于肠外、皮下、静脉、肌肉、腹腔内、透皮、口腔、鞘内、颅内、鼻腔或外用途径给药。

[0157] 鉴于本发明的化合物或其药物组合物可用于制备S1PR调节剂，本发明还提供了在受试者体内调节S1PR的方法，包括将有效量的本发明化合物、或其旋光异构体或药学上可接受的盐或药物组合物给予有此需要的受试者。在具体的实施方式中，所述方法是在受试者体内激动S1PR4的方法；更优选地，所述方法在受试者体内激动S1PR4，而不激动S1PR1。

[0158] 本发明的优点：

[0159] 1.本发明提供的化合物是一种结构全新的S1PR调节剂，特别是S1PR4选择性受体调节剂；

[0160] 2.本发明提供的化合物对S1PR4及S1PR4突变蛋白具有优异的生物活性；

[0161] 3.本发明提供的化合物为开发能靶向S1PR4靶标的药物奠定了基础，具备极大的产业化和商品化前景以及市场价值，经济效益显著。

[0162] 以下结合具体实施案例对本发明的技术方案进一步描述，但以下实施案例不构成对本发明的限制，所有依据本发明的原理和技术手段采用的各种施用方法，均属于本发明范围。下列实施例中未注明具体条件的实验方法，通常按照常规条件，或按照制造厂商所建议的条件。除非另外说明，否则百分比和份数按重量计算。

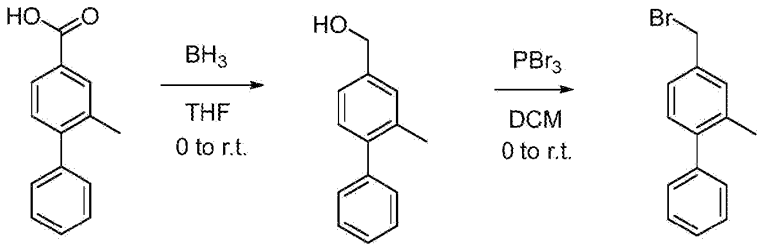
[0163] 材料与方法

[0164] 本发明的化合物的合成如下所示：

[0165] 实施例1

[0166] 化合物的合成

[0167] 4-(溴甲基)-2-甲基-1,1’-联苯的合成

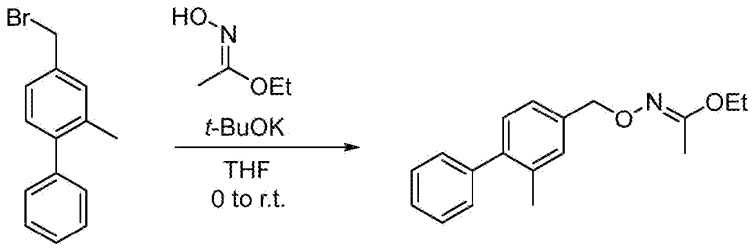


[0168] 将3-甲基-4-苯基苯甲酸(2.00g，9.40mmol)溶解于10mL无水四氢呋喃中，置于冰浴下搅拌。将1.0M的硼烷四氢呋喃溶液(14mL，14.20mmol)逐滴加入。滴完恢复室温搅拌。2小时后反应完全，逐滴加水进行淬灭，然后二氯甲烷进行萃取。饱和食盐水洗涤。合并有机相，用无水硫酸钠干燥，减压浓缩得无色油状物1.50g，收率80.6%，产物不需进一步纯化直接用于下一步。LC-MS(ESI):m/z:199.1 $(M+H)^+$.

[0169] 将(2-甲基-[1,1’-联苯]-4-基)甲醇(1.50g，7.60mmol)溶解于10mL二氯甲烷中，冰浴下滴加三溴化磷(820mg，3.10mmol)，滴加完毕恢复室温搅拌，0.5小时后反应完全。加水淬灭后用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥，减压浓缩得无色油状物1.80g，收率91.0%。

[0170] ^{1}H NMR(400MHz,DMSO-d_6) δ 7.45(dd,J＝14.9,7.9Hz,2H),7.39-7.30(m,5H),7.18(d,J＝7.8Hz,1H),4.72(s,2H),2.21(s,3H).LC-MS(ESI):m/z:261.3$(M+H)^+$.

[0171] (E)-N-((2-甲基-[1,1’-联苯]-4-基)甲氧基)乙酰氨基甲酸乙酯的合成

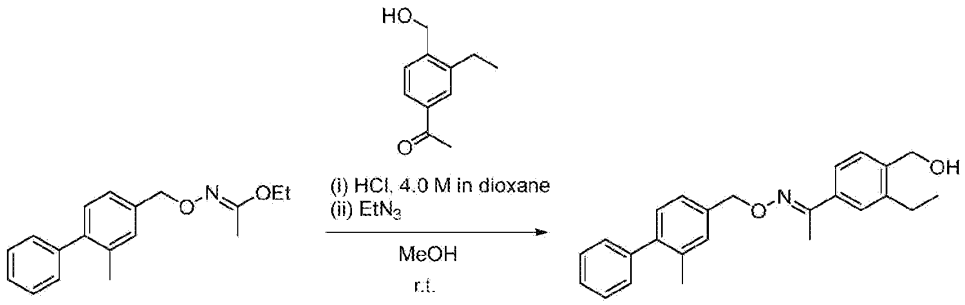


[0172] 将乙酰羟肟酸乙酯(400mg，3.90mmol)溶解于10mL四氢呋喃溶液中，然后置于冰浴下。向反应体系中滴加1.0M的叔丁醇钾四氢呋喃溶液(15.2mL，15.20mmol)。滴加完毕继续在冰浴下搅拌0.5小时。将4-(溴甲基)-2-甲基-1,1’-联苯(1.01g，3.90mmol)溶解于5mL四氢呋喃中，然后滴加到反应体系中。滴加完毕恢复到室温搅拌，TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱

和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩，过硅胶柱得油状无色液体821mg，收率74.4%。

[0173] ^{1}H NMR(400MHz,DMSO−d_6) δ 7.43(t,J＝7.3Hz,2H),7.38−7.30(m,3H),7.27−7.16(m,3H),4.89(s,2H),3.95(q,J＝7.5Hz,2H),2.22(s,3H),1.90(s,3H),1.20(t,J＝7.5Hz,3H).

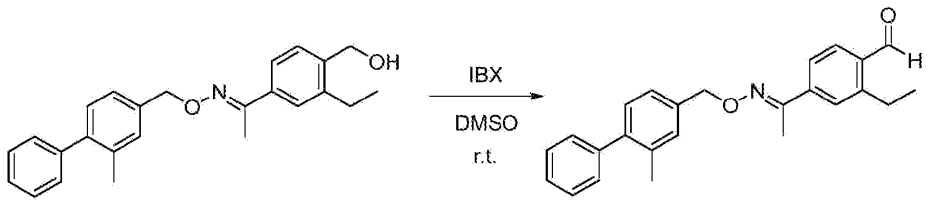
[0174] (E)−1−(3−乙基−4−(羟甲基)苯基)乙烷−1−酮O−((2−甲基−1,1'−联苯]−4−基)甲基)肟的合成



[0175] 将(E)−N−((2−甲基−[1,1’−联苯]−4−基)甲氧基)乙酰氨基甲酸乙酯(200mg，0.70mmol)溶解于5mL甲醇中。滴加4.0M的氯化氢二氧六环溶液(0.4mL，0.30mmol)到反应液中。搅拌0.5小时后滴加三乙胺调节pH＝4−6之间。然后将1−(3−乙基−4−(羟甲基)苯基)乙酮(125mg，0.70mmol)溶解于2mL甲醇中滴加到反应体系中。TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体140mg，收率53.6%。

[0176] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.46(s,1H),7.42(dd,J＝8.0,1.6Hz,1H),7.36−7.27(m,4H),7.29−7.18(m,3H),7.18−7.06(m,2H),5.18(s,2H),4.66(s,2H),2.65(q,J＝7.5Hz,2H),2.21(s,3H),1.50(s,3H),1.18(t,J＝7.5Hz,3H).

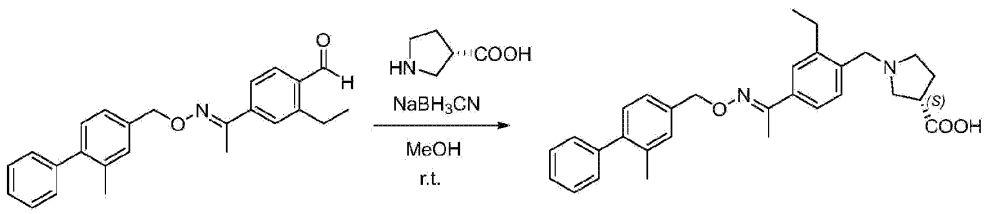
[0177] (E)−2−乙基−4−(1−((2−甲基−[1,1’−联苯]−4−基)甲氧基)亚氨基乙基)苯甲醛的合成



[0178] 将(E)-1-(3-乙基-4-(羟甲基)苯基)乙烷-1-酮O-((2-甲基-[1,1’-联苯]-4-基)甲基)肟(112mg，0.30mmol)溶解在3mL的DMSO溶剂中。加入2-碘酰苯甲酸(IBX)氧化剂(84mg，0.30mmol)。然后室温搅拌大约2小时。TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩得油状无色液体99mg，收率89.1%。

[0179] ^{1}H NMR(400MHz,$CDCl_3$) δ 10.29(s,1H),7.82(d,J=6.4Hz,1H),7.64(dd,J=12.9,5.5Hz,1H),7.60(d,J=9.7Hz,1H),7.40(dd,J=18.7,11.4Hz,2H),7.36-7.30(m,5H),7.25-7.19(m,1H),5.29(s,2H),3.09(q,J=7.5Hz,2H),2.31(s,3H),2.30(s,3H),1.33(t,J=7.5Hz,3H).

[0180] (S,E)-1-(2-乙基-4-(1-((2-甲基-[1,1’-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸的合成(化合物30)

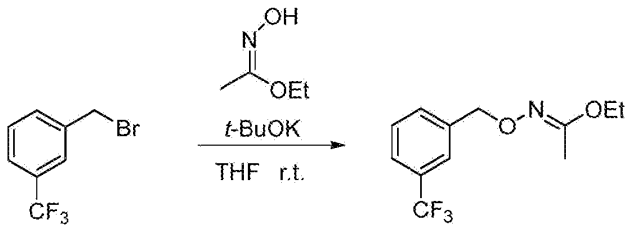


[0181] 将(E)-2-乙基-4-(1-((2-甲基-[1,1’-联苯]-4-基)甲氧基)亚氨基乙基)苯甲醛(74mg，0.20mmol)溶解于5mL的甲醇中加入1滴乙酸，然后加入S-吡咯烷3-甲酸(35mg，0.30mmol)。室温搅拌3分钟后加入氰基硼氢化钠(19mg，0.30mmol)。TLC监测反应进度。反应完全后将反应体系减压蒸馏，加入水和二氯甲烷进行萃取。饱和食盐水洗涤，合并有机相并用无水硫酸钠干燥后浓缩过硅胶柱，得白色固体29mg，收率30.8%。

[0182] ^{1}H NMR(400MHz,CD_3OD) δ 7.57(s,1H),7.51(d,J=8.0Hz,1H),7.44-7.35(m,3H),7.33-7.26(m,5H),7.17(d,J=7.7Hz,1H),5.20(s,2H),4.02(s,2H),3.19(t,J=8.6Hz,1H),3.11-3.00(m,3H),2.90(dd,J=17.2,7.9Hz,1H),2.79(q,J=7.5Hz,2H),2.26(s,3H),2.24(s,3H),2.15(dd,J=14.6,7.3Hz,2H),1.23(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 179.95,154.70,143.25,141.79,141.48,137.08,136.62,134.91,130.01,129.84,129.31,128.79,127.77,126.49,126.28,125.37,123.57,75.60,57.40,55.54,53.76,44.56,28.06,25.20,19.22,14.48,11.50.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{30}H_{34}N_2O_3$,471.2648；found:471.2650.HPLC Purity:98.16%,retention time:1.52min.

[0183] 代表性化合物13的合成路线如下：

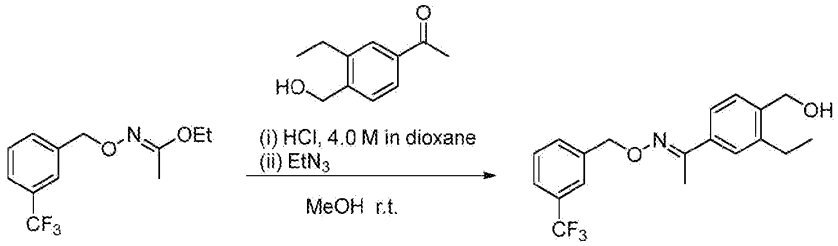
[0184] (E)-N-((3-(三氟甲基)苄基)氧基)乙酰氨基甲酸乙酯的合成



[0185] 将乙酰羟肟酸乙酯(865mg，8.40mmol)溶解于10mL四氢呋喃溶液中，然后置于冰浴下。向反应体系中滴加1.0M的叔丁醇钾四氢呋喃溶液(17mL，16.70mmol)。滴加完毕继续在冰浴下搅拌0.5小时。将3-(三氟甲基)溴苄(1.99g，8.40mmol)溶解于5mL四氢呋喃中，然后滴加到反应体系中。滴加完毕恢复到室温搅拌，TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体1.81g，收率82.6%。

[0186] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.63(s,1H),7.54(d,J=7.1Hz,2H),7.45(t,J=7.7Hz,1H),4.97(s,2H),3.98(q,J=7.1Hz,2H),1.95(s,3H),1.24(t,J=7.1Hz,3H).

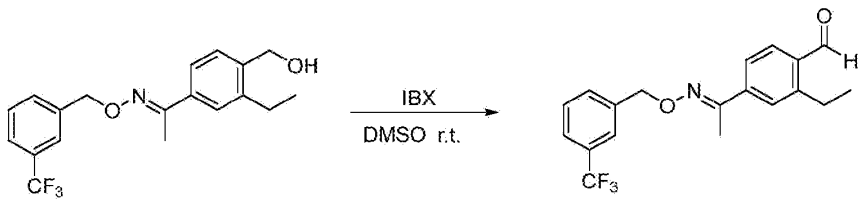
[0187] (E)-1-(3-乙基-4-羟甲基)苯基)乙烷-1-酮O-(3-(三氟甲基)苄基)肟的合成



[0188] 将(E)-N-((3-(三氟甲基)苄基)氧基)乙酰氨基甲酸乙酯(157mg，0.60mmol)溶解于5mL甲醇中。滴加4.0M的氯化氢二氧六环溶液0.4mL到反应液中。搅拌0.5小时后滴加三乙胺调节pH=4-6之间。然后将1-(3-乙基-4-(羟甲基)苯基)乙酮(107mg，0.60mmol)溶解于2mL甲醇中滴加到反应体系中。TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体150mg，收率71.1%。

[0189] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.69(s,1H),7.59(dd,J＝12.7,7.9Hz,3H),7.51−7.46(m,2H),7.37(d,J＝8.0Hz,1H),5.28(s,2H),4.74(s,1H),4.72(s,2H),2.71(q,J＝7.6Hz,2H),2.28(s,3H),1.24(t,J＝7.5Hz,3H).

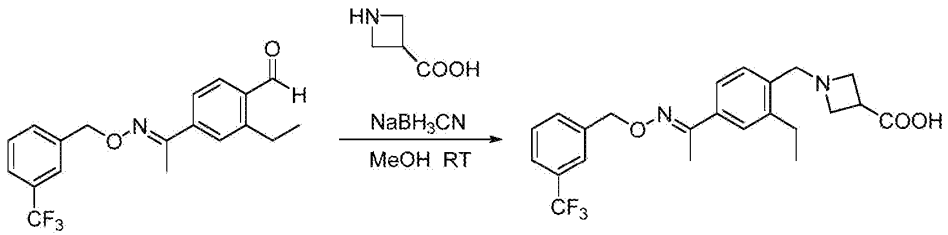
[0190] (E)−2−乙基−4−(1−(((3−(三氟甲基)苯基)氧)亚氨基)乙基)苯甲醛的合成



[0191] 将(E)−1−(3−乙基−4−羟甲基)苯基)乙烷−1−酮O−(3−(三氟甲基)苄基)肟(211mg，0.60mmol)溶解在3mL的DMSO溶剂中。加入IBX氧化剂(308mg，1.10mmol)。然后室温搅拌大约2小时。TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体126mg，收率60.0%。

[0192] ^{1}H NMR(400MHz,$CDCl_3$) δ 10.29(s,1H),7.82(d,J＝8.1Hz,1H),7.69(s,1H),7.64−7.53(m,4H),7.50(d,J＝7.7Hz,1H),5.31(s,2H),3.08(d,J＝7.5Hz,2H),2.30(s,3H),1.28(t,J＝7.5Hz,3H).

[0193] (E)−1−(2−乙基−4−(1−((3−(三氟甲基)苯基)氧)亚氨基)乙基)苄基)氮杂环丁烷−3−羧酸(化合物13)的合成



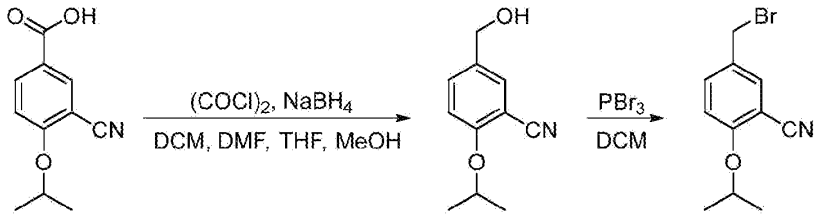
[0194] 将(E)−2−乙基−4−(1−(((3−(三氟甲基)苯基)氧)亚氨基)乙基)苯甲醛(105mg，0.30mmol)溶解于5mL的甲醇中加入1滴乙酸，然后加入3−吖丁啶羧酸(61mg，0.60mmol)。室温搅拌 3分钟后加入氰基硼氢化钠(38mg，0.60mmol)。TLC监测反应进度。反应完全后将反应体系减压蒸馏，加入适量的水，用二氯甲烷进行萃取，

饱和食盐水洗涤，合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状物78mg，收率60.0%。

[0195] ^{1}H NMR(400MHz,CD_3OD) δ 7.71(s,1H),7.67(d,J=7.4Hz,1H),7.62-7.51(m,3H),7.47(dd,J=8.0,1.6Hz,1H),7.31(d,J=8.0Hz,1H),5.28(s,2H),3.98(s,2H),3.83(t,J=8.8Hz,2H),3.67(t,J=8.4Hz,2H),3.28(dd,J=15.2,6.9Hz,1H),2.73(q,J=7.5Hz,2H),2.26(s,3H),1.21(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.20,155.32,142.88,139.73,136.16,133.52,131.41,130.23(q,J=32.0Hz),128.87,128.82,126.17,124.32,124.31(q,J=272.0Hz),124.06,123.61,74.70,57.68,35.94,25.11,14.28,11.47.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{23}H_{25}F_3N_2O_3$,435.1896；found:435.1897.HPLC Purity:99.79%,retention time:1.17min.

[0196] 代表性化合物16的合成路线如下所示：

[0197] 5-(溴甲基)-2-异丙氧基苯甲腈的合成



[0198] 将2.0M的草酰氯二氯甲烷溶液(14.6mL，29.20mmol)加到3-氰基-4-(异丙氧基)苯甲酸(2.01g，9.80mmol)中并加入一滴DMF。将反应混合物在室温搅拌0.5小时，然后减压浓缩。将3-氰基-4-(异丙氧基)苯甲酰氯(923mg，4.50mmol)在10mL四氢呋喃中溶解并冷却至0℃，加入硼氢化钠(414mg，11.20mmol)，接着加入2mL甲醇并将反应混合物在0℃下搅拌20分钟，然后升温至室温。2小时后，用1.0M盐酸将反应混合物酸化至pH=3。水层用乙酸乙酯萃取，合并有机层并用无水硫酸钠干燥，浓缩得无色油状物1.12g，收率59.9%。

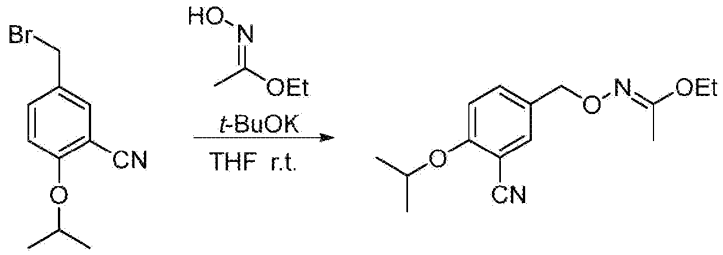
[0199] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.48(s,1H),7.47(d,J=12Hz,1H),7.45(s,1H),6.92(d,J=8.6Hz,1H),4.61(dt,J=12.2,6.2Hz,1H),4.57(s,2H),1.36(d,J=6.1Hz,6H).

[0200] 将5-(羟基甲基)-2-异丙氧基苯甲腈(993mg，5.20mmol)溶解于10mL二氯甲烷中，冰浴下滴加三溴化磷(0.2mL，2.10mmol)，滴加完毕恢复室温搅拌，0.5小时

后反应完全。加水淬灭后用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥，浓缩得无色油状物1.19g，收率90.5%。

[0201] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.56(d,J=2.1Hz,1H),7.51(dd,J=8.7,2.2Hz,1H),6.92(d,J=8.7Hz,1H),4.65(dt,J=12.0,6.0Hz,1H),4.42(s,2H),1.39(d,J=6.1Hz,6H).

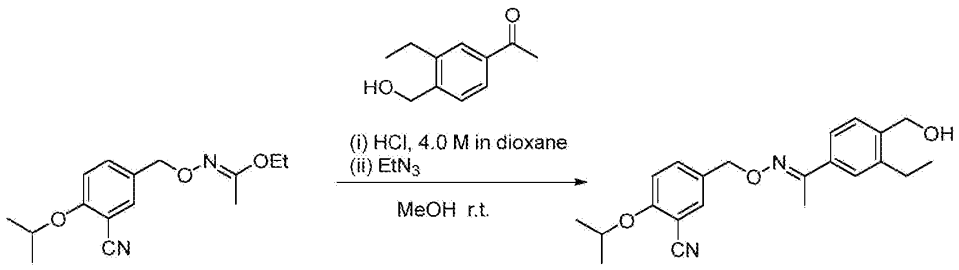
[0202] 乙基-N-((3-氰基-4-(异丙氧基)苄基)氧)乙酰氨基甲酸酯的合成



[0203] 将乙酰羟肟酸乙酯(402mg，3.90mmol)溶解于10mL四氢呋喃溶液中，然后置于冰浴下。向反应体系中滴加1.0M的叔丁醇钾四氢呋喃溶液(8.0mL，8.00mmol)，滴加完毕继续在冰浴下搅拌0.5小时。将3-氰基-4-异丙氧基溴苄(987mg，3.90mmol)溶解于5mL四氢呋喃中，然后滴加到反应体系中。滴加完毕恢复到室温搅拌，TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体619mg，收率57.5%。

[0204] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.54(d,J=2.0Hz,1H),7.48(dd,J=8.7,2.1Hz,1H),6.92(d,J=8.7Hz,1H),4.82(s,2H),4.64(dt,J=12.1,6.1Hz,1H),3.97(q,J=7.1Hz,2H),1.92(s,3H),1.39(d,J=6.1Hz,6H),1.24(t,J=7.1Hz,3H).

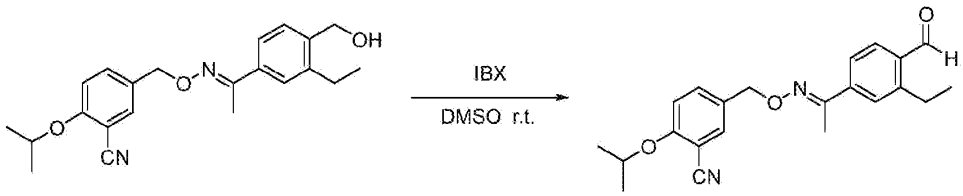
[0205] (E)-1-(3-乙基-4-(羟甲基)苯基)乙烷-1-酮-O-(3-氰基-4-(异丙氧基)苄基)肟的合成



[0206] 将乙基-N-((3-氰基-4-(异丙氧基)苄基)氧)乙酰氨基甲酸酯(138mg，0.50mmol)溶解于5mL甲醇中。滴加4.0M的氯化氢二氧六环溶液(0.4mL，0.30mmol)到反应液中。搅拌0.5小时后滴加三乙胺调节pH＝4-6之间。然后将1-(3-乙基-4-(羟甲基)苯基)乙酮(90mg，0.50mmol)溶解于2mL甲醇中滴加到反应体系中。TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷进行萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体127mg，收率69.3%。

[0207] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.61(d,J＝2.0Hz,1H),7.54(dd,J＝8.7,2.1Hz,1H),7.45(dd,J＝12.1,4.1Hz,2H),7.38(d,J＝7.9Hz,1H),6.94(d,J＝8.7Hz,1H),5.13(s,2H),4.73(s,2H),4.64(dt,J＝12.1,6.0Hz,1H),2.72(q,J＝7.6Hz,2H),2.24(s,3H),1.40(d,J＝6.1Hz,6H),1.24(t,J＝7.6Hz,3H).

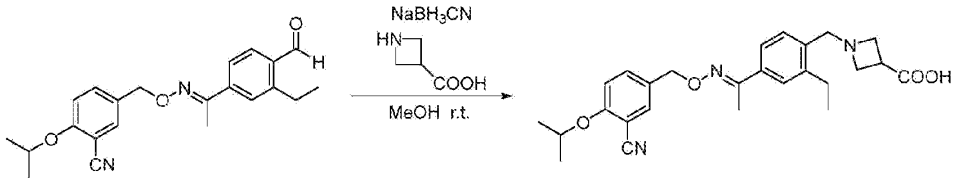
[0208] (E)-5-((((1-(3-乙基-4-甲酰苯基)亚乙基)氨基)氧)甲基)-2-异丙氧基苯腈的合成



[0209] 将(E)-1-(3-乙基-4-(羟甲基)苯基)乙烷-1-酮-O-(3-氰基-4-(异丙氧基)苄基)肟(147mg，0.40mmol)溶解在4mL的DMSO溶剂中，加入IBX氧化剂(225mg，0.80mmol)。室温搅拌大约2小时，TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体119mg，收率81.2%。

[0210] ^{1}H NMR(400MHz,$CDCl_3$) δ 10.28(s,1H),7.82(d,J＝8.1Hz,1H),7.65-7.58(m,2H),7.58-7.50(m,2H),6.95(d,J＝8.7Hz,1H),5.16(s,2H),4.65(dt,J＝12.1,6.1Hz,1H),3.08(q,J＝7.5Hz,2H),2.26(s,3H),1.40(d,J＝6.1Hz,6H),1.28(t,J＝7.5Hz,3H).

[0211] (E)-1-(2-乙基-4-(1-((3-氰基-4-(异丙氧基)苄基)氧基)亚氨基)乙基)苄基)氮杂环丁烷-3-羧酸(化合物16)的合成

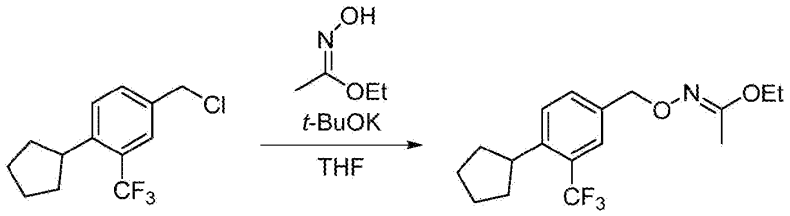


[0212] 将(E)-5-((((1-(3-乙基-4-甲酰苯基)亚乙基)氨基)氧)甲基)-2-异丙氧基苯腈(109mg，0.30mmol)溶解于5mL的甲醇中加入1滴乙酸，然后加入3-吖丁啶羧酸(61mg，0.60mmol)。室温搅拌3分钟后加入氰基硼氢化钠(19mg，0.30mmol)。TLC监测反应进度。反应完全后将反应体系减压蒸馏，加入水和二氯甲烷进行萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得浅色固体70mg，收率52.3%。

[0213] ^{1}H NMR(400MHz,CD_3OD) δ 7.64(d,J=6.7Hz,2H),7.56(s,1H),7.50(dd,J=8.0,1.6Hz,1H),7.33(d,J=8.1Hz,1H),7.16(d,J=9.4Hz,1H),5.14(s,2H),4.78-4.73(m,1H),4.18(s,2H),3.99(t,J=9.3Hz,2H),3.90(t,J=8.6Hz,2H),3.40-3.33(m,1H),2.76(q,J=7.5Hz,2H),2.23(s,3H),1.38(s,3H),1.37(s,3H),1.23(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.23,159.53,154.92,143.23,136.96,134.67,133.44,131.00,129.23,126.42,123.80,116.06,113.66,101.88,74.22,71.68,57.49,56.20,35.40,25.12,20.71,14.38,11.39.HRMS(ESI)(m/z):[M+H]$^{+}$calcd for $C_{26}H_{31}N_3O_4$,450.2396；found:450.2395.HPLC Purity:96.46%,retention time:1.02min.

[0214] 化合物17的合成路线如下所示：

[0215] (E)-N-((4-环戊基-3-(三氟甲基)苄基)氧)乙酰氨基甲酸乙酯的合成

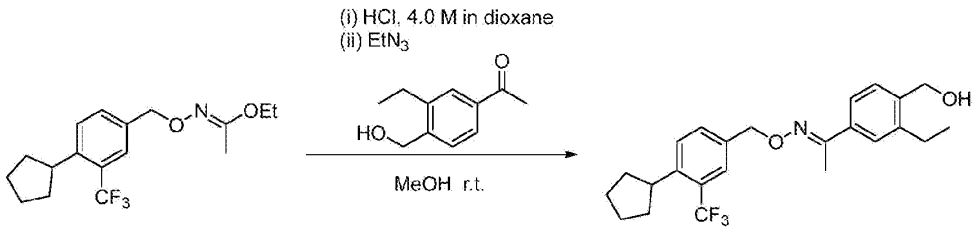


[0216] 将乙酰羟肟酸乙酯(196mg，1.90mmol)溶解于5mL四氢呋喃溶液中，然后置于冰浴下。向反应体系中滴加1.0M的叔丁醇钾四氢呋喃溶液(4mL，3.90mmol)，滴加完毕继续在冰浴下搅拌0.5小时。将4-氯甲基-1-环戊基-2-三氟甲基苯(498mg，1.90mmol)溶解于3mL四氢呋喃中，然后滴加到反应体系中。滴加完毕恢复到

室温搅拌，TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷进行萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体532mg，收率85.1%。

[0217] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.59(s,1H),7.48(d,J=8.4Hz,1H),7.43(d,J=8.1Hz,1H),4.91(s,2H),3.99(q,J=7.1Hz,2H),3.41−3.28(m,1H),2.07(m,2H),1.94(s,3H),1.89−1.80(m,2H),1.73−1.68(m,2H),1.63−1.56(m,2H),1.25(t,J=7.1Hz,3H).

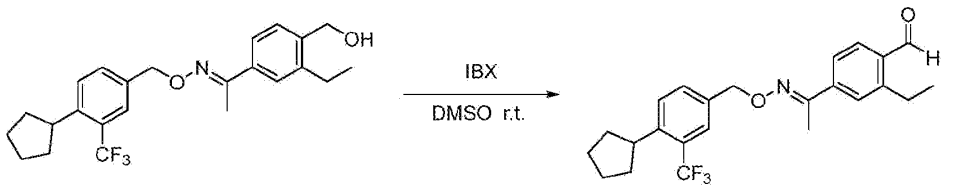
[0218] (E)−1−(3−乙基−4−(羟甲基)苯基)乙烷−1−酮−O−(4−环戊基−3−(三氟甲基)苄基)肟的合成



[0219] 将(E)−N−((4−环戊基−3−(三氟甲基)苄基)氧)乙酰氨基甲酸乙酯(461mg，1.40mmol)溶解于5mL甲醇中。滴加4.0M的氯化氢二氧六环溶液(1.0mL，0.70mmol)到反应液中。搅拌0.5小时后滴加三乙胺调节pH=4−6之间。然后将1−(3−乙基−4−(羟甲基)苯基)乙酮(267mg，1.50mmol)溶解于2mL甲醇中滴加到反应体系中。TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷进行萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得油状无色液体489mg，收率83.4%。

[0220] ^{1}H NMR(400MHz,$CDCl_3$) δ 7.66(s,1H),7.54(d,J=8.0Hz,1H),7.49(d,J=6.2Hz,1H),7.45(d,J=8.6Hz,2H),7.38(t,J=8.6Hz,1H),5.22(s,2H),4.72(s,2H),3.36(p,J=8.5Hz,1H),2.71(q,J=7.6Hz,2H),2.22(s,3H),2.14−2.04(m,2H),1.92−1.81(m,2H),1.77−1.69(m,2H),1.61−1.56(m,2H),1.25(t,J=7.1Hz,3H).

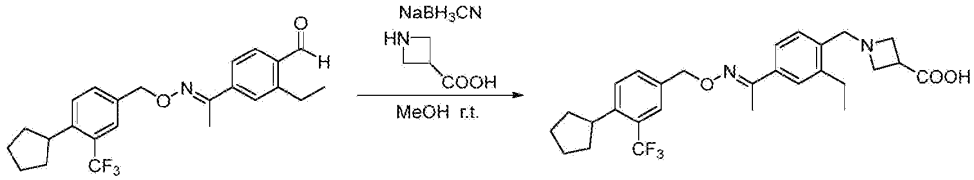
[0221] (E)−4−(1−((4−环戊基−3−(三氟甲基)苄基)氧基)亚氨基)乙基)−2−乙基苯甲醛的合成



[0222] 将(E)-1-(3-乙基-4-(羟甲基)苯基)乙烷-1-酮-O-(4-环戊基-3-(三氟甲基)苄基)肟(503mg，1.20mmol)溶解在3mL的DMSO溶剂中。加入IBX氧化剂(952mg，2.40mmol)，然后室温搅拌大约2小时。TLC监测反应进度。反应完成后加水淬灭反应，用二氯甲烷萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后过硅胶柱，得油状无色液体302mg，60.3%。

[0223] ^{1}H NMR(400MHz,$CDCl_3$) δ 10.29(s,1H),7.82(d,J=8.1Hz,1H),7.69-7.59(m,2H),7.59-7.52(m,2H),7.47(d,J=8.1Hz,1H),5.25(s,2H),3.45-3.30(m,1H),3.08(q,J=7.5Hz,2H),2.28(s,3H),2.07(d,J=12.3Hz,2H),1.88-1.80(m,2H),1.73-1.70(m,2H),1.64-1.54(m,2H),1.28(t,J=7.1Hz,3H).

[0224] (E)-1-(4-(1-((4-环戊基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)-2-乙基苄基)氮杂环丁烷-3-羧酸(化合物17)的合成



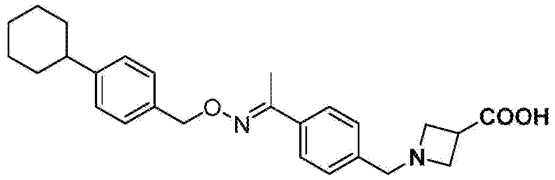
[0225] 将(E)-4-(1-((4-环戊基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)-2-乙基苯甲醛(500mg，1.20mmol)溶解于5mL的甲醇中加入1滴乙酸，然后加入3-吖丁啶羧酸(242mg，2.40mmol)。室温搅拌3分钟后加入氰基硼氢化钠(113mg，1.80mmol)。TLC监测反应进度。反应完全后将反应体系减压蒸馏，加入适量水，用二氯甲烷进行萃取，饱和食盐水洗涤。合并有机相用无水硫酸钠干燥后浓缩过硅胶柱，得浅色固体182mg，收率30.2%。

[0226] ^{1}H NMR(400MHz,CD_3OD) δ 7.64(s,1H),7.53(dt,J=9.8,5.1Hz,4H),7.38(t,J=11.5Hz,1H),5.22(s,2H),4.25(s,2H),4.02(d,J=8.3Hz,4H),3.43-3.33(m,1H),2.75(dd,J=15.0,7.5Hz,2H),2.29-2.14(s,3H),2.03(m,2H),1.93-1.81(m,2H),1.78-1.57(m,4H),1.20(t,J=7.

1Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.79,154.79,145.36,143.28,137.08,136.13,131.80,130.92,129.27,127.96,127.80(q,J＝28.7Hz),126.46,124.78(q,J＝273.5Hz),124.76,123.84,74.79,57.14,40.91,35.57,25.62,25.20,14.36,11.42.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{28}H_{33}F_3N_2O_3$,503.2522；found:503.2523.HPLC Purity:96.46%,retention time:2.28min.

[0227] 其他化合物的反应条件和以上化合物类似。

[0228] (E)-1-(4-(1-((4-环己基苄基)氧基)亚氨基)乙基)苄基)氮杂环丁-3-羧酸(化合物1)



[0229] ^{1}H NMR(400MHz,Methanol-d_4) δ 7.60(d,J＝8.3Hz,2H),7.30(dd,J＝8.2,2.7Hz,4H),7.19(d,J＝8.1Hz,2H),5.14(s,2H),3.64(d,J＝2.4Hz,2H),3.53(t,J＝8.1Hz,2H),3.38－3.32(m,2H),3.20(dd,J＝16.6,8.2Hz,1H),2.57－2.45(m,1H),2.22(s,3H),1.84(d,J＝9.2Hz,4H),1.75(d,J＝12.2Hz,1H),1.43(d,J＝4.4Hz,6H).^{13}C NMR(151MHz,Methanol-d_4) δ 154.60,147.52,138.04,135.64,135.45,128.59,128.01,126.36,125.82,75.68,62.35,57.58,44.40,36.48,34.30,29.46,26.62,25.86,11.45.LC-MS(ESI):m/z:421.1$(M+H)^+$.

[0230] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)苄基)氮杂环丁烷-3-羧酸(化合物2)

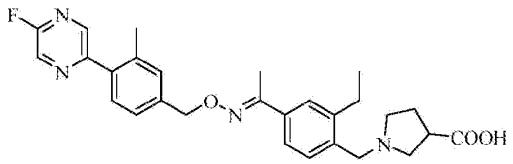
[0231] ^{1}H NMR(400MHz,Methanol-d_4) δ 7.56(d,J＝17.6Hz,1H),7.53(d,J＝7.4Hz,1H),7.39(t,J＝12.5Hz,1H),7.30(d,J＝7.9Hz,2H),7.19(d,J＝7.9Hz,2H),5.11(s,2H),4.31(s,2H),4.10(dd,J＝21.9,12.7Hz,2H),4.02(t,J＝8.4Hz,2H),3.35(s,3H),2.78-2.70(m,2H),1.49-1.36(m,9H).LC-MS(ESI):m/z:431.1$(M+H)^+$.

[0232] (E)-1-(4-(1-((4-环己基苄基)氧基)亚氨基)乙基)-2-乙基苄基)氮杂环丁-3-羧酸(化合物3)

[0233] ^{1}H NMR(400MHz,DMSO) δ 8.36(s,1H),8.04(dt,J＝28.8,6.4Hz,4H),7.71－7.46(m,4H),4.38-4.33(m,2H),4.10-4.01(m,2H),3.59-3.55(m,2H),2.85－2.76(m,2H),2.79(q,J＝

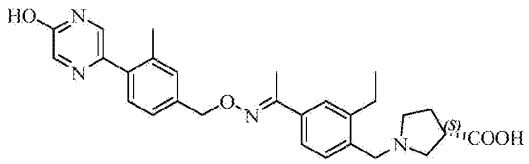
7.5Hz,2H),2.57 - 2.45(m,1H),1.24-1.21(m,3H),1.20(t,J=7.5Hz,3H).LC-MS(ESI):m/z:449.1(M+H)$^+$.

[0234] (E)-1-(2-乙基-4-(1-(((4-(5-氟吡嗪-2-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物4)的结构



[0235] 淡黄色固体，产率18.4%^{1}H NMR(500MHz,Methanol-d$_4$) δ 8.58(dd,J=8.3,1.3Hz,1H),8.37(d,J=1.5Hz,1H),7.64(d,J=1.9Hz,1H),7.58(dd,J=8.1,1.9Hz,1H),7.49(d,J=8.1Hz,1H),7.42(d,J=7.8Hz,1H),7.40 - 7.35(m,2H),5.26(s,2H),4.40(s,2H),3.53(dd,J=11.2,5.8Hz,1H),3.39 - 3.35(m,2H),3.28(dd,J=11.0,7.4Hz,1H),3.15 - 3.06(m,1H),2.82(q,J=7.5Hz,2H),2.37(s,3H),2.34 - 2.22(m,5H),1.26(t,J=7.5Hz,3H).^{13}C NMR(126MHz,Methanol-d$_4$) δ 177.85,160.27,158.28,154.49,152.90,143.73,141.29,141.22,139.46,137.74,136.37,135.08,131.94,131.64,130.48,130.33,130.21,129.58,126.66,125.50,123.97,75.34,56.55,54.38,53.52,43.60,27.72,25.23,19.04,14.55,11.40.MS(ESI)(m/z):[M+H]$^+$491.25.

[0236] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(5-羟基吡嗪-2-基)-苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸的合成(化合物5)的结构



[0237] 黄色固体，产率72.5%。^{1}H NMR(500MHz,Methanol-d4) δ 8.17(d,J=1.4Hz,1H),7.67(d,J=1.8Hz,1H),7.61(dd,J=8.1,1.9Hz,1H),7.57(d,J=8.1Hz,1H),7.51(d,J=1.4Hz,1H),7.35(d,J=8.1Hz,2H),7.33 - 7.29(m,1H),5.24(s,2H),4.53(s,2H),3.70 - 3.57(m,2H),3.51 - 3.43(m,2H),3.38(q,J=8.6,8.2Hz,1H),2.85(q,J=7.5Hz,2H),2.49 - 2.41(m,1H),2.38(s,3H),2.36 - 2.30(m,1H),2.29(s,3H),1.27(t,J=7.5Hz,3H).^{13}C NMR(126MHz,Methanol-d4) δ 154.34,143.95,138.49,138.17,136.24,135.20,130.78,130.24,129.10,129.01,1

26.79,125.48,124.11,75.49,55.17,54.38,53.64,27.07,25.36,19.14,14.60,11.39.MS(m/z):[M+H]$^+$489.20

[0238] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物6)

[0239] ^{1}H NMR(400MHz,Methanol-d4) δ 7.70 - 7.63(m,3H),7.57(d,J=16.3Hz,2H),7.44(d,J=8.2Hz,2H),5.22(s,2H),3.96(d,J=5.7Hz,2H),3.35(s,2H),3.16-3.12(m,1H),3.05-2.98(m,2H),2.95 - 2.82(m,2H),2.26(s,3H),2.16(d,J=8.0Hz,2H),1.82-1.80(m,,2H),1.78-1.75(m,3H),1.58-1.45(m,6H).LC-MS(ESI):m/z:503.1(M+H)$^+$.

[0240] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)苄基)哌啶-3-羧酸(化合物7)

[0241] ^{1}H NMR(400MHz,Methanol-d4) δ 7.70 - 7.63(m,3H),7.57(d,J=16.3Hz,2H),7.44(d,J=8.2Hz,2H),5.22(s,2H),3.96(d,J=5.7Hz,2H),3.35(s,2H),3.16-3.12(m,1H),3.05-2.98(m,2H),2.95 - 2.82(m,2H),2.26(s,3H),2.16(d,J=8.0Hz,2H),1.82-1.80(m,,2H),1.78-1.75(m,3H),1.58-1.45(m,8H).LC-MS(ESI):m/z:517.2(M+H)$^+$.

[0242] (E)-4-((4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)苄基)氨基)丁酸(化合物8)

[0243] ^{1}H NMR(400MHz,Methanol-d4) δ 7.65(d,J=8.1Hz,3H),7.58(t,J=10.4Hz,1H),7.53(d,J=8.1Hz,1H),7.41(t,J=10.5Hz,2H),5.21(s,2H),3.88(s,2H),2.91(t,J=11.2Hz,1H),2.76(t,J=7.1Hz,2H),2.30 - 2.17(m,5H),1.85-1.75(m,6H),1.61 - 1.29(m,6H).LC-MS(ESI):m/z:491.2(M+H)$^+$.

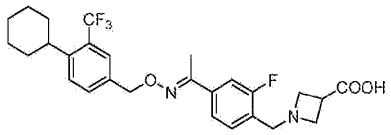
[0244] (E)-3-((4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)苄基)氨基)环己烷-1-羧酸(化合物9)

[0245] ^{1}H NMR(400MHz,Methanol-d4) δ 7.77 - 7.32(m,7H),5.21(s,2H),3.91(s,2H),2.91(s,1H),2.68(s,1H),2.25(s,3H),2.18-2.15(m,2H),1.88-1.70(m,9H),1.65 - 1.33(m,8H).^{13}C NMR(151MHz,MeOD) δ 182.91,155.03,146.14,136.31,135.59,131.60,128.55,128.47,128.10,125.97,124.84,124.79,74.73,55.54,49.13,45.59,40.06,34.19,31.24,29.43,26.60,25.70,11.40.LC-MS(ESI):m/z:531.2(M+H)$^+$.

[0246] (E)-3-((4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)苄基)氨基)丙酸(化合物10)

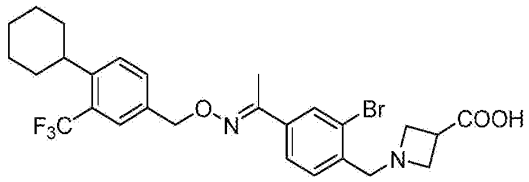
[0247] ^{1}H NMR(400MHz,Methanol-d4) δ 7.65(d,J=7.4Hz,3H),7.56(dd,J=24.3,8.1Hz,2H),7.39(d,J=8.0Hz,2H),5.21(s,2H),3.90(s,2H),2.95-2.90(m,3H),2.44(t,J=6.6Hz,2H),2.25(s,3H),1.87(d,J=16.6Hz,2H),1.78(d,J=11.1Hz,3H),1.48(ddd,J=33.8,22.3,10.1Hz,5H).^{13}C NMR(151MHz,Methanol-d4) δ 178.44,154.94,146.14,137.98,136.30,135.86,131.60,128.53,128.10,126.03,124.84,124.79,74.74,51.72,45.19,40.06,35.04,34.18,26.59,25.70,11.38.LC-MS(ESI):m/z:478.2(M+H)$^{+}$.

[0248] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基)氧)亚氨基)乙基)-2-氟苄基)氮杂环丁-3-羧酸(化合物11)的结构



[0249] 白色固体，产率40.6%，熔点：144.6-144.9℃。^{1}H NMR(400MHz,$CDCl_3$) δ 7.74-7.27(m,6H),5.26(s,2H),3.97(s,2H),3.80(d,J=8.2Hz,2H),3.72-3.67(m,3H),2.94-2.90(m,1H),2.27(s,3H),1.94-1.82(m,2H),1.80-1.75(m,2H),1.56-1.50(m,2H),1.45-1.40(m,4H).HRMS(ESI)(m/z):[M+H]$^{+}$calcd for $C_{27}H_{30}F_4N_2O_3$,507.2271；found:507.2270.HPLC Purity:91.98%,retention time:2.26min.

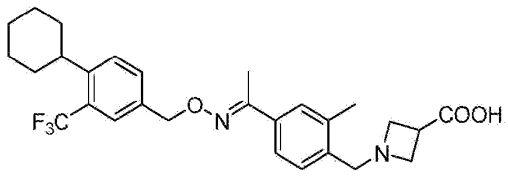
[0250] (E)-1-(2-溴-4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)氮杂环丁烷-3-羧酸(化合物12)的结构



[0251] 白色固体，产率40.6%，熔点：131.6-131.9℃。^{1}H NMR(400MHz,CD_3OD) δ 7.91(d,J=1.6Hz,1H),7.69-7.63(m,2H),7.63-7.49(m,2H),7.45(d,J=8.1Hz,1H),5.23(s,2H),4.08(s,2H),3.87(t,J=8.6Hz,2H),3.75(t,J=8.2Hz,2H),2.93-2.86(m,2H),2.30(s,3H),1.84-1.80(m,2H),1.77-1.70(m,3H),1.60-1.34(m,5H).^{13}C NMR(151MHz,CD_3OD) δ

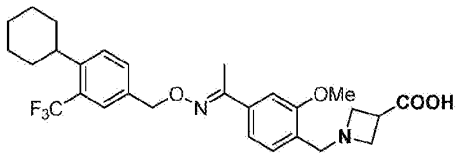
178.85,154.09,147.89,146.25,138.90,131.73,129.72,129.46,128.84,128.53,128.16,127.33,124.97,121.07,112.36,90.94,74.97,61.53,58.01,40.07,34.17,26.69,25.70,12.97.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{27}H_{30}BrF_3N_2O_3$,567.1470；found:567.1473.HPLC Purity:90.25%,retention time:2.87min.

[0252] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基)氧)亚氨基)乙基)-2-甲基苄基)氮杂环丁-3-羧酸(化合物18)的结构



[0253] 白色固体，产率40.6%，熔点：155.1-155.6℃。^{1}H NMR(400MHz,CD_3OD) δ 7.64(d,J=5.9Hz,1H),7.59-7.42(m,4H),7.37-7.29(m,1H),5.20(s,2H),4.05(s,2H),3.91(t,J=8.9Hz,2H),3.77(dd,J=17.0,8.5Hz,2H),3.60(dd,J=14.1,7.1Hz,1H),2.91(t,J=11.3Hz,1H),2.39(s,3H),2.23(s,3H),1.88-1.80(m,2H),1.79-1.70(m,3H),1.46-1.39(m,5H).^{13}C NMR(151MHz,CD_3OD) δ 178.49,154.91,146.15,138.90,136.99,136.37,131.61,128.89,128.52,128.11,127.91,127.31,124.88,124.80(q,J=273.5Hz),123.68,74.75,57.59,40.05,35.70,34.18,34.13,26.59,25.70,17.99,16.97,11.38.HRMS(ESI)(m/z):[M+H]+calcd for $C_{28}H_{33}F_3N_2O_3$,503.2522；found:503.2523.HPLC Purity:94.29%,retention time:2.57min.

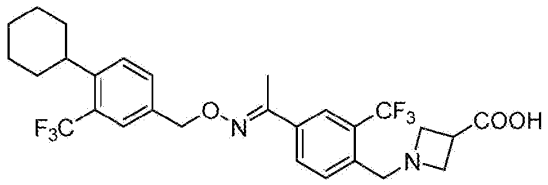
[0254] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基)氧)亚氨基)乙基)-2-甲氧基苄基)氮杂环丁-3-羧酸(化合物27)的结构



[0255] 白色固体，产率40.6%，熔点：145.2-145.6℃。^{1}H NMR(400MHz,CD_3OD) δ 7.66(s,1H),7.64-7.49(m,3H),7.25(t,J=8.7Hz,2H),5.21(s,2H),3.84(s,3H),3.70(s,2H),3.59(d,J=8.2Hz,2H),3.52(t,J=8.0Hz,1H),3.42(t,J=8.2Hz,2H),2.91(d,J=10.6Hz,1H),2.23(s,3H),1.92-1.83(m,2H),1.79-1.87(m,3H),1.63-1.48(m,5H).^{13}C NMR(151MHz,CD_3OD) δ 175.87,157.76,154.59,146.26,139.82,138.93,136.16,131.75,128.55,127.30,127.0

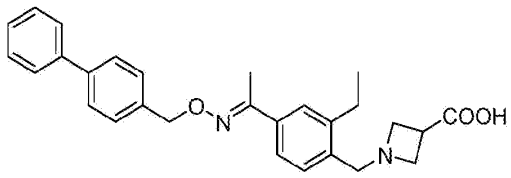
1,124.98,124.80(q,J＝273.5Hz),119.36,118.66,107.91,74.92,60.20,57.19,54.77,40.06,34.72,34.18,26.58,25.69,11.39.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{28}H_{33}F_3N_2O_4$,519.2471；found:519.2473.HPLC Purity:96.28%,retention time:1.27min.

[0256] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)-2-(三氟甲基)苄基)氮杂环丁-3-羧酸(化合物19)的结构



[0257] 白色固体，产率40.6%，熔点：135.6-138.9℃。^{1}H NMR(400MHz,CD_3OD) δ 7.98(s,1H),7.88(d,J＝8.1Hz,1H),7.69-7.51(m,4H),5.24(s,2H),3.96(s,2H),3.73(t,J＝8.3Hz,2H),3.53(t,J＝8.0Hz,2H),3.29-3.19(m,1H),2.92(t,J＝11.3Hz,1H),1.86-1.80(m,2H),1.78-1.70(m,3H),1.62-1.35(m,5H).^{13}C NMR(151MHz,CD_3OD) δ 178.45,153.61,146.30,138.92,135.99,135.83,131.79,129.85,129.41,128.52,128.15,127.29,125.06,124.77(q,J＝273.5Hz),124.22(q,J＝273.6Hz),123.02,75.08,58.10,57.75,40.06,36.07,34.17,26.59,25.70,11.05.LC-MS(ESI):m/z:557.2(M+H)$^+$.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{28}H_{30}F_6N_2O_3$,557.2239；found:557.2237.HPLC Purity:97.16%,retention time:2.56min.

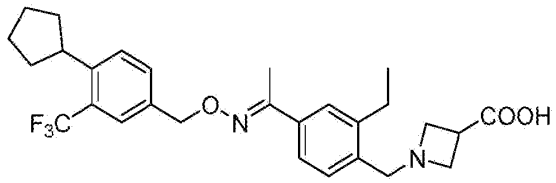
[0258] (E)-1-(4-(1-(([1,1'-联苯]-4-基甲氧基)亚氨基)乙基)-2-乙基苄基)氮杂环丁烷-3-羧酸(化合物20)的结构



[0259] 白色固体，产率40.6%，熔点：120.3-121.9℃。^{1}H NMR(400MHz,CD_3OD) δ 7.64-7.53(m,4H),7.49-7.39(m,6H),7.36-7.23(m,2H),5.24(s,2H),3.76(s,2H),3.67-3.58(m,2H),3.42(t,J＝8.1Hz,2H),3.29-3.15(m,1H),2.72(q,J＝7.5Hz,2H),2.23(s,3H),1.22(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 179.26,155.07,142.50,140.80,140.59,137.27,135.67,135.39,129.45,128.52,128.44,128.33,126.93,126.58,126.55,126.52,126.50,12

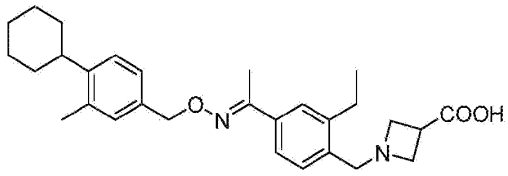
5.94,123.39,75.38,58.84,57.94,36.49,25.11,14.23,11.55.LC-MS(ESI):m/z:443.2(M+H)$^+$.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{28}H_{30}N_2O_3$,443.2335；found:443.2337.HPLC Purity:98.03%,retention time:1.30min.

[0260] (E)-1-(4-(1-((4-环戊基-3-(三氟甲基)苄基)氧)亚氨基)乙基)-2-乙基苄基)氮杂环丁-3-羧酸(化合物17)的结构



[0261] 浅色固体，产率30.2%，熔点：131.7-133.2℃。^{1}H NMR(400MHz,CD_3OD) δ 7.64(s,1H),7.53(dt,J=9.8,5.1Hz,4H),7.38(t,J=11.5Hz,1H),5.22(s,2H),4.25(s,2H),4.02(d,J=8.3Hz,4H),3.43-3.33(m,1H),2.75(dd,J=15.0,7.5Hz,2H),2.29-2.14(s,3H),2.03(m,2H),1.93-1.81(m,2H),1.78-1.57(m,4H),1.20(t,J=7.1Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.79,154.79,145.36,143.28,137.08,136.13,131.80,130.92,129.27,127.96,127.80(q,J=28.7Hz),126.46,124.78(q,J=273.5Hz),124.76,123.84,74.79,57.14,40.91,35.57,25.62,25.20,14.36,11.42.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{28}H_{33}F_3N_2O_3$,503.2522；found:503.2523.HPLC Purity:96.46%,retention time:2.28min.

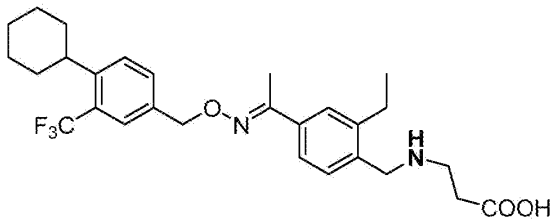
[0262] (E)-1-(4-(1-((4-环己基-3-甲基苄基)氧)亚氨基)乙基)-2-乙基苄基)氮杂环丁烷-3-羧酸(化合物24)的结构



[0263] 黄色固体，产率33.3%，熔点：135.8-136.3℃。^{1}H NMR(400MHz,CD_3OD) δ 7.53(s,1H),7.47(dd,J=8.0,1.5Hz,1H),7.30(d,J=8.1Hz,1H),7.15(d,J=8.5Hz,3H),5.11(s,2H),4.00(s,2H),3.84(t,J=8.8Hz,2H),3.69(t,J=8.4Hz,2H),3.30-3.22(m,1H),2.82-2.60(m,3H),2.29(s,3H),2.20(s,3H),1.83-1.80(m,2H),1.76-1.72(m,3H),1.48-1.29(m,5H),1.21(t,J=7.8Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.12,154.47,145.22,142.85,136.5

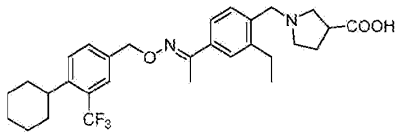
4,134.88,134.61,133.03,129.89,128.89,126.20,125.88,124.96,123.61,75.80,57.62,57.34,39.83,35.88,33.49,26.85,26.03,25.14,18.10,14.33,11.49.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{29}H_{38}N_2O_3$,463.2961；found:463.2962.HPLC Purity:98.19%,retention time:2.39min.

[0264] (E)-3-((4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)-2-乙基苄基)氨基)丙酸(化合物25)



[0265] ^{1}H NMR(400MHz,CD_3OD) δ 7.65(s,1H),7.58(dd,J=11.7,7.9Hz,2H),7.51(t,J=9.5Hz,2H),7.46 - 7.35(m,1H),5.21(s,2H),4.19(s,2H),3.18(t,J=6.3Hz,2H),3.07(t,J=6.4Hz,1H),2.91(t,J=11.3Hz,1H),2.78(q,J=7.5Hz,2H),2.51(t,J=6.3Hz,2H),2.24(s,3H),1.83-1.80(m,2H),1.77-1.70(m,3H),1.59 - 1.33(m,5H).^{13}C NMR(151MHz,CD_3OD) δ 177.24,154.83,146.18,143.23,137.30,136.22,131.68,131.45,129.89,128.13,127.19,127.00,126.43,124.96,124.91,123.96,74.81,44.84,40.06,34.19,33.03,32.12,26.59,25.70,25.07,14.37,11.42.LC-MS(ESI):m/z:505.2$(M+H)^+$.

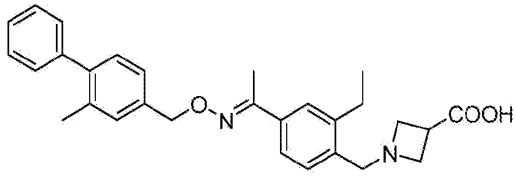
[0266] (E)-1-(4-(1-((4-环己基-3-(三氟甲基)苄基)氧基)亚氨基)乙基)-2-乙基苄基)吡咯烷-3-羧酸(化合物26)



[0267] ^{1}H NMR(400MHz,CD_3OD) δ 7.65(s,1H),7.59(d,J=7.2Hz,2H),7.53(d,J=7.5Hz,2H),7.45(d,J=8.1Hz,1H),5.22(s,2H),4.33(s,2H),3.40-3.42(m,1H),3.38 - 3.32(m,1H),3.25(t,J=6.9Hz,2H),3.11 - 3.00(m,1H),2.91(t,J=11.3Hz,1H),2.80(q,J=7.5Hz,2H),2.24(s,3H),1.85(d,J=11.7Hz,2H),1.77(d,J=11.9Hz,3H),1.59 - 1.50(m,2H),1.46 - 1.31(m,3H),1.27(t,J=7.1Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.42,154.79,146.19,143.65,1

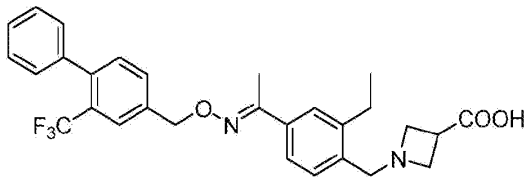
37.44,136.23,131.68,130.98,130.40,128.13,127.20,127.01,126.59,125.71,124.95,124.91,123.91,74.82,56.80,54.66,53.60,43.92,40.06,34.18,26.59,25.69,25.21,14.51,11.39.LC-MS(ESI):m/z:531.3$(M+H)^+$.

[0268] (E)-1-(2-乙基-4-(1-((2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)氮杂环丁烷-3-羧酸(化合物22)的结构



[0269] 白色固体，产率40.6%，熔点：154.2-154.8℃。^{1}H NMR(400MHz,CD_3OD) δ 7.55(s,1H),7.49(d,J=8.0Hz,1H),7.38(t,J=7.3Hz,2H),7.34-7.23(m,6H),7.15(d,J=7.7Hz,1H),5.17(s,2H),4.00(s,2H),3.84(t,J=8.7Hz,2H),3.69(t,J=8.3Hz,2H),3.27-3.20(m,1H),2.74(q,J=7.5Hz,2H),2.24(s,3H),2.23(s,3H),1.21(q,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.15,154.69,142.88,141.76,141.46,137.05,136.48,134.91,133.09,129.85,129.32,128.92,128.79,127.78,126.51,126.21,125.39,123.63,75.61,57.61,57.33,35.89,25.15,19.26,14.34,11.52.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{29}H_{32}N_2O_3$,457.2492；found:457.2493.HPLC Purity:91.98%,retention time:2.30min.

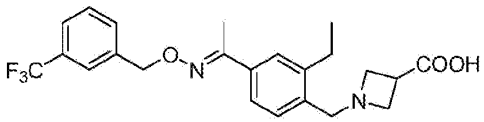
[0270] (E)-1-(2-乙基-4-(1-((2-(三氟甲基)-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)氮杂环丁烷-3-羧酸(化合物21)的结构



[0271] 白色固体，产率40.6%，熔点：155.5-155.9℃。^{1}H NMR(400MHz,CD_3OD) δ 7.69(d,J=12.3Hz,1H),7.56(t,J=8.1Hz,1H),7.49(s,1H),7.42(d,J=8.0Hz,1H),7.26(dd,J=5.3,2.9Hz,4H),7.22(d,J=7.8Hz,1H),7.19-7.13(m,2H),5.21(s,2H),4.11(s,2H),3.93(t,J=9.1Hz,2H),3.83(t,J=8.4Hz,2H),3.29-3.22(m,1H),2.66(q,J=7.5Hz,2H),2.16(s,3H),1.12(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.22,155.11,143.30,140.77,139.59,

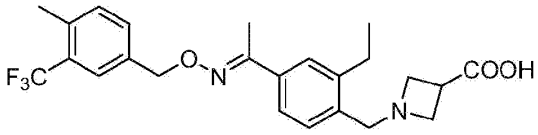
138.22,136.91,132.05,131.31,130.97,129.29,128.64,127.87(q,J＝29.8Hz),127.46,127.37,126.45,125.32,124.23(q,J＝273.8Hz),123.86,74.64,57.34,55.98,35.39,25.18,14.40,11.50.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{29}H_{29}F_3N_2O_3$,511.2209；found:511.2211.HPLC Purity:97.71%,retention time:1.56min.

[0272] (E)-1-(2-乙基-4-(1-((3-(三氟甲基)苯基)氧)亚氨基)乙基)苄基)氮杂环丁烷-3-羧酸(化合物13)的结构



[0273] 淡黄色油状，产率60.0%。^{1}H NMR(400MHz,CD_3OD) δ 7.71(s,1H),7.67(d,J＝7.4Hz,1H),7.62-7.51(m,3H),7.47(dd,J＝8.0,1.6Hz,1H),7.31(d,J＝8.0Hz,1H),5.28(s,2H),3.98(s,2H),3.83(t,J＝8.8Hz,2H),3.67(t,J＝8.4Hz,2H),3.28(dd,J＝15.2,6.9Hz,1H),2.73(q,J＝7.5Hz,2H),2.26(s,3H),1.21(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.20,155.32,142.88,139.73,136.16,133.52,131.41,130.23(q,J＝32.0Hz),128.87,128.82,126.17,124.32,124.31(q,J＝272.0Hz),124.06,123.61,74.70,57.68,35.94,25.11,14.28,11.47.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{23}H_{25}F_3N_2O_3$,435.1896；found:435.1897.HPLC Purity:99.79%,retention time:1.17min.

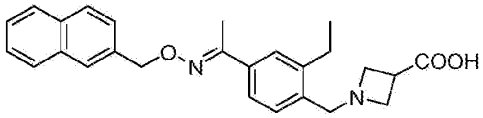
[0274] (E)-1-(2-乙基-4-(1-((4-甲基-3-(三氟甲基)苄基)氧)亚氨基)乙基)氮杂环丁烷-3-羧酸(化合物14)的结构



[0275] 淡黄色油状，产率21.3%。^{1}H NMR(400MHz,CD_3OD) δ 7.67(s,1H),7.57(s,1H),7.52(t,J＝7.9Hz,2H),7.35(dd,J＝12.5,8.1Hz,2H),5.22(s,2H),4.22(s,2H),3.97(dd,J＝22.5,8.5Hz,4H),3.40-3.33(m,1H),2.76(q,J＝7.5Hz,2H),2.47(s,3H),2.25(s,3H),1.22(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.72,155.00,143.07,136.62,136.50,135.81,132.36,131.84,131.45,129.07,128.29(q,J＝30.2Hz),126.30,125.10,124.70(q,J＝273.3Hz),123.70,74.70,57.55,56.78,35.67,25.12,17.72,14.32,11.40.HRMS(ESI)(m/z):[M+H]$^+$calcd

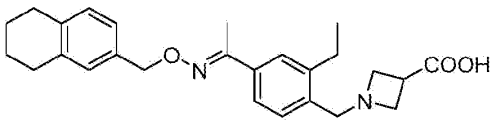
for $C_{24}H_{27}F_3N_2O_3$,449.2052；found:449.2050.HPLC Purity:99.32%,retention time:1.35min.

[0276] (E)-1-(2-乙基-4-(1-((萘-2-基甲氧基)亚氨基)乙基)氮杂环丁烷-3-羧酸(化合物15)的结构



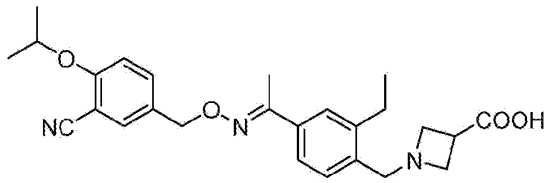
[0277] 白色固体，产率25.9%，熔点：131.5-131.7℃。^{1}H NMR(400MHz,CD_3OD) δ 7.89-7.79(m,4H),7.61-7.51(m,2H),7.52-7.41(m,3H),7.35-7.18(m,1H),5.40(s,2H),3.95(s,2H),3.80(t,J=8.6Hz,2H),3.61(dt,J=10.7,5.9Hz,2H),3.29-3.22(m,1H),2.77-2.59(m,2H),2.27(s,3H),1.25-1.14(m,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.73,154.96,142.81,136.31,135.65,133.40,133.14,128.83,127.62,127.55,127.29,126.58,126.18,125.78,125.74,125.59,123.60,75.84,57.73,36.00,25.11,14.28,11.53.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{26}H_{28}N_2O_3$,417.2179；found:417.2179.HPLC Purity:98.77%,retention time:1.24min.

[0278] (E)-1-(2-乙基-4-(1-(((5,6,7,8-四氢萘-2-基)甲氧基)亚氨基)乙基)苄基)氮杂环丁烷-3-羧酸(化合物23)的结构



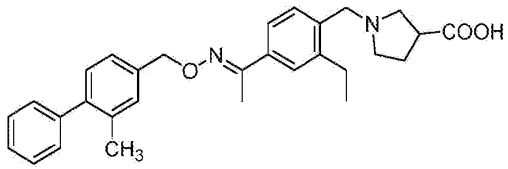
[0279] 白色固体，产率10.2%，熔点：135.3-138.9℃。^{1}H NMR(400MHz,CD_3OD) δ 7.50(s,1H),7.44(dd,J=8.0,1.5Hz,1H),7.28(d,J=8.0Hz,1H),7.13-7.05(m,2H),7.00(d,J=7.7Hz,1H),5.09(s,2H),3.83(s,2H),3.70(t,J=8.3Hz,2H),3.51(t,J=8.2Hz,2H),3.24(dd,J=16.6,8.3Hz,1H),2.78-2.71(m,6H),2.20(s,3H),1.80-1.70(m,4H),1.23(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.90,154.68,142.58,136.56,136.32,136.01,134.99,134.56,128.69,128.62,128.61,126.00,125.26,123.45,75.81,58.35,57.83,36.29,29.01,28.78,25.11,23.06,14.25,11.51.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{26}H_{32}N_2O_3$,421.2492；found: 421.2492.HPLC Purity:98.54%,retention time:1.48min.

[0280] (E)-1-(4-(1-(((3-氰基-4-异丙氧基苄基)氧)亚氨基)乙基)-2-乙基苄基)氮杂环丁烷-3-羧酸(化合物16)的结构



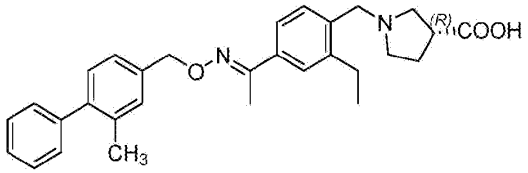
[0281] 淡黄色固体，产率52.3%，熔点：112.6-112.9℃。^{1}H NMR(400MHz,CD_3OD) δ 7.64(d,J=6.7Hz,2H),7.56(s,1H),7.50(dd,J=8.0,1.6Hz,1H),7.33(d,J=8.1Hz,1H),7.16(d,J=9.4Hz,1H),5.14(s,2H),4.78-4.73(m,1H),4.18(s,2H),3.99(t,J=9.3Hz,2H),3.90(t,J=8.6Hz,2H),3.40-3.33(m,1H),2.76(q,J=7.5Hz,2H),2.23(s,3H),1.38(s,3H),1.37(s,3H),1.23(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.23,159.53,154.92,143.23,136.96,134.67,133.44,131.00,129.23,126.42,123.80,116.06,113.66,101.88,74.22,71.68,57.49,56.20,35.40,25.12,20.71,14.38,11.39.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{26}H_{31}N_3O_4$,450.2396；found:450.2395.HPLC Purity:96.46%,retention time:1.02min.

[0282] (E)-1-(2-乙基-4-(1-((2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物28)的结构



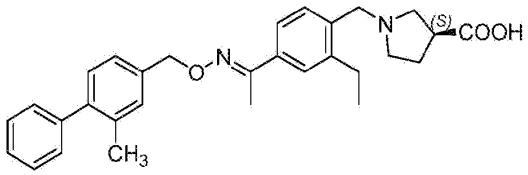
[0283] 灰褐色固体，产率30.1%，熔点：144.3-146.4℃。^{1}H NMR(600MHz,CD_3OD) δ 7.62(s,1H),7.55(dd,J=8.0,1.6Hz,1H),7.47(dd,J=14.4,6.3Hz,1H),7.41-7.35(m,2H),7.33-7.28(m,2H),7.26(dd,J=5.0,3.2Hz,3H),7.14(d,J=7.7Hz,1H),5.20(s,2H),4.29(s,2H),3.47-3.35(m,1H),3.34-3.30(m,2H),3.24(t,J=7.1Hz,2H),3.03-3.09(m,1H),2.80(q,J=7.5Hz,2H),2.31-2.27(m,1H),2.25(s,3H),2.22(s,3H),1.20(t,J=7.1Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.58,154.38,143.61,141.73,141.47,137.53,137.03,134.92,130.99,130.41,129.86,129.34,128.79,127.79,126.57,126.52,125.40,123.90,75.69,56.76,54.66,53.58,43.99,27.89,25.26,19.27,14.57,11.48.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{30}H_{34}N_2O_3$,471.2648；found:471.2647.HPLC Purity:96.16%,retention time:1.66min.

[0284] (R,E)-1-(2-乙基-4-(1-((2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物29)的结构



[0285] 白色固体，产率14.9%，熔点：149.6-150.6℃。^{1}H NMR(400MHz,CD_3OD) δ 7.60(s,1H),7.54(d,J=8.0Hz,1H),7.45(d,J=8.0Hz,1H),7.38(t,J=7.3Hz,2H),7.34-7.18(m,5H),7.14(d,J=7.7Hz,1H),5.20(s,2H),4.26(s,2H),3.42-3.29(m,3H),3.20(t,J=7.1Hz,2H),3.09-2.97(m,1H),2.79(q,J=7.5Hz,2H),2.30-2.27(m,1H),2.24(s,3H),2.22(s,3H),1.22(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.63,154.39,143.55,141.74,141.47,137.42,137.04,134.92,131.32,130.35,129.85,129.33,128.79,127.78,126.53,126.51,125.39,123.85,75.68,56.79,54.73,53.59,44.01,27.89,25.24,19.26,14.55,11.47.HRMS(ESI)(m/z):[M+H]$^{+}$calcd for $C_{30}H_{34}N_2O_3$,471.2648；found:471.2650.HPLC Purity:97.51%,retention time:1.45min.

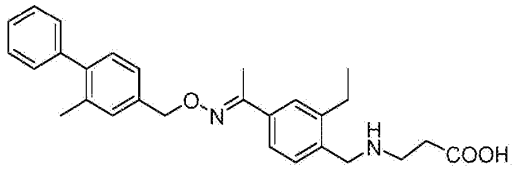
[0286] (S,E)-1-(2-乙基-4-(1-((2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物30)的结构



[0287] 白色固体，产率31.8%，熔点：145.6-148.9℃。^{1}H NMR(400MHz,CD_3OD) δ 7.57(s,1H),7.51(d,J=8.0Hz,1H),7.44-7.35(m,3H),7.33-7.26(m,5H),7.17(d,J=7.7Hz,1H),5.20(s,2H),4.02(s,2H),3.19(t,J=8.6Hz,1H),3.11-3.00(m,3H),2.90(dd,J=17.2,7.9Hz,1H),2.79(q,J=7.5Hz,2H),2.26(s,3H),2.24(s,3H),2.15(dd,J=14.6,7.3Hz,2H),1.23(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 179.95,154.70,143.25,141.79,141.48,137.08,136.62,134.91,130.01,129.84,129.31,128.79,127.77,126.49,126.28,125.37,123.57,75.60,57.40,55.54,53.76,44.56,28.06,25.20,19.22,14.48,11.50.HRMS(ESI)(m/z):[M+H]$^{+}$ca

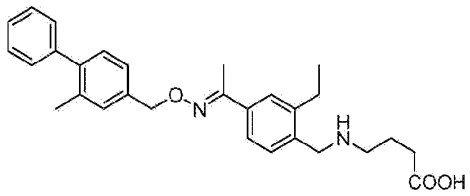
lcd for $C_{30}H_{34}N_2O_3$,471.2648；found:471.2650.HPLC Purity:98.16%,retention time:1.52min.

[0288] (E)-3-((2-乙基-4-(1-((2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)胺)丙烷酸(化合物31)的结构



[0289] 白色固体，产率22.4%，熔点：149.6-149.8℃。^{1}H NMR(400MHz,CD_3OD) δ 7.66(s,1H),7.60(d,J=8.1Hz,1H),7.43(dd,J=17.6,7.9Hz,3H),7.36-7.28(m,5H),7.19(d,J=7.7Hz,1H),5.24(s,2H),4.28(s,2H),3.25(t,J=6.2Hz,2H),2.83(q,J=7.5Hz,2H),2.60-2.47(m,2H),2.28(s,3H),2.25(s,3H),1.29(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 176.80,154.30,143.38,141.76,141.51,137.84,137.02,134.93,130.29,130.06,129.85,129.31,128.78,127.78,126.55,126.52,125.39,124.05,75.71,44.64,31.36,25.08,21.94,19.22,14.38,11.40.HRMS(ESI)(m/z):$[M+H]^+$calcd for $C_{28}H_{32}N_2O_3$,445.2491；found:445.2490.HPLC Purity:99.29%,retention time:1.24min.

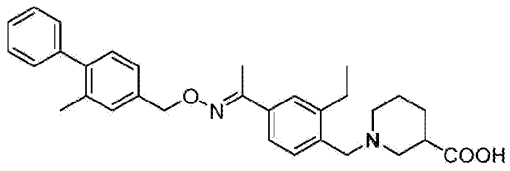
[0290] (E)-4-((2-乙基-4-(1-((2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)氨基丁酸(化合物32)的结构



[0291] 白色固体，产率13.2%，熔点：133.3-136.3℃。^{1}H NMR(400MHz,CD_3OD) δ 7.63(s,1H),7.58(d,J=8.1Hz,1H),7.49-7.36(m,3H),7.36-7.28(m,5H),7.17(d,J=7.7Hz,1H),5.21(s,2H),4.21(s,2H),3.15(t,J=6.2Hz,2H),2.79(q,J=7.5Hz,2H),2.45-2.37(m,2H),2.26(s,3H),2.24(s,3H),1.90-1.85(m,2H),1.26(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 176.86,154.32,143.24,141.77,141.51,137.67,137.04,134.93,130.46,129.84,129.80,129.31,128.78,127.78,126.52,126.48,125.38,124.04,75.70,35.68,25.21,21.93,21.44,1

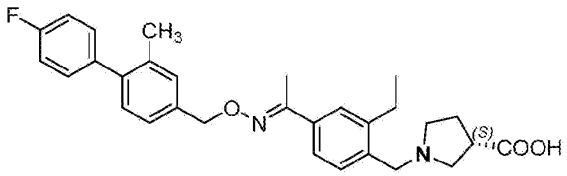
9.22,14.36,11.40.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{29}H_{34}N_2O_3$,459.2648；found:459.2647.HPLC Purity:98.69%,retention time:1.34min.

[0292] (E)-1-(2-乙基-4-(1-((2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)哌啶-3-羧酸(化合物33)的结构



[0293] 淡黄色油状，产率15.3%。^{1}H NMR(400MHz,CD_3OD) δ 7.61(s,1H),7.56(d,J=8.0Hz,1H),7.50-7.37(m,3H),7.36-7.28(m,5H),7.22-7.09(m,1H),5.23(s,2H),4.12(s,2H),3.22-2.88(m,4H),2.83(q,J=7.5Hz,2H),2.61(s,1H),2.27(s,3H),2.25(s,3H),1.79-1.70(m,4H),1.31-1.19(m,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.19,154.48,143.99,141.75,141.48,137.42,137.05,134.92,130.86,129.85,129.32,128.81,128.79,128.77,127.79,126.51,125.39,123.77,75.67,57.43,55.07,52.96,25.22,22.28,19.25,14.48,11.48.HRMS(ESI)(m/z):[M+H]$^+$calcd for $C_{31}H_{36}N_2O_3$,485.2804；found:485.2802.HPLC Purity:97.56%,retention time:1.42min.

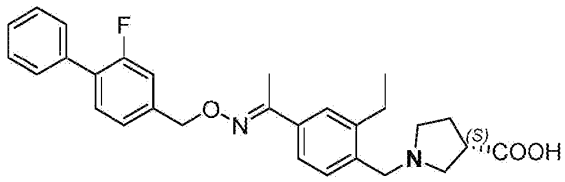
[0294] (S,E)-1-(2-乙基-4-(1-(((4'-氟-2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物34)的结构



[0295] 淡黄色固体，产率11.3%。^{1}H NMR(600MHz,CD_3OD) δ 7.64(d,J=1.9Hz,1H),7.58(dd,J=8.1,1.9Hz,1H),7.47(d,J=8.1Hz,1H),7.33-7.25(m,4H),7.19-7.10(m,3H),5.22(s,2H),4.42-4.34(m,2H),3.53-3.47(m,1H),3.38-3.32(m,2H),3.29-3.24(m,1H),3.12-3.04(m,1H),2.82(q,J=7.5Hz,2H),2.32(dt,J=14.2,7.9Hz,1H),2.27(s,3H),2.24(s,3H),2.23-2.18(m,1H),1.26(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.91,162.81,161.19,154.29,143.70,140.39,137.84,137.27,135.04,130.62,130.56,130.44,129.88,129.37,114.

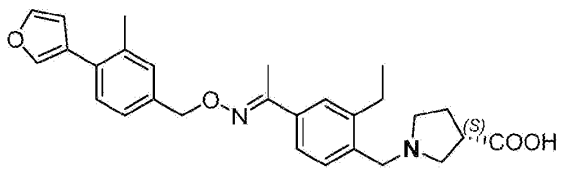
54,114.40,75.64,56.64,54.50,53.58,43.83,27.74,25.22,19.19,14.54,11.38.MS(ESI)(m/z):[M+H]$^+$489.25.

[0296] (S,E)−1−(2−乙基−4−(1−(((2−氟−[1,1'−联苯]−4−基)甲氧基)亚氨基)乙基)苄基)吡咯烷−3−羧酸(化合物35)的结构



[0297] 淡黄色固体，产率18.7%。^{1}H NMR(600MHz,CD_3OD) δ 7.63(s,1H),7.57(d,J=6.1Hz,1H),7.52(d,J=8.0Hz,2H),7.48 – 7.40(m,4H),7.35(t,J=7.4Hz,1H),7.28(d,J=9.4Hz,1H),7.22(d,J=11.5Hz,1H),5.26(s,2H),4.33(d,J=4.1Hz,2H),3.46(dd,J=11.1,5.8Hz,1H),3.34(d,J=11.2Hz,2H),3.25(t,J=9.0Hz,1H),3.07(ddd,J=14.5,8.6,5.8Hz,1H),2.81(q,J=7.5Hz,2H),2.29(s,4H),2.22(dq,J=13.0,6.4Hz,1H),1.24(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.47,159.53,154.78,143.69,135.54,130.42,130.38,128.61,128.58,128.09,127.35,126.66,123.95,123.69,123.66,115.10,114.94,74.70,56.65,54.60,53.63,43.70,27.76,25.22,14.52,11.42.MS(ESI)(m/z):[M+H]$^+$475.30.

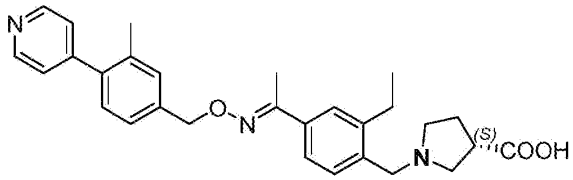
[0298] (S,E)−1−(2−乙基−4−(1−(((4−(呋喃−3−基)−3−甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷−3−羧酸(化合物36)的结构



[0299] 淡黄色固体，产率21.2%。^{1}H NMR(600MHz,CD_3OD) δ 7.61(dd,J=13.5,1.8Hz,2H),7.56 – 7.53(m,2H),7.47(d,J=8.1Hz,1H),7.30(d,J=7.8Hz,1H),7.27(s,1H),7.23(dd,J=7.8,1.8Hz,1H),6.62(d,J=1.9Hz,1H),5.18(s,2H),4.44 – 4.28(m,2H),3.52(dd,J=11.3,5.7Hz,1H),3.40 – 3.36(m,1H),3.35 – 3.32(m,1H),3.27(dt,J=11.1,7.4Hz,1H),3.08(ddd,J=14.4,8.8,5.7Hz,1H),2.80(q,J=7.5Hz,2H),2.36(s,3H),2.30(dt,J=15.6,7.0Hz,1H),2.24(s,3H),2.22(dd,J=13.5,6.2Hz,1H),1.23(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.76,154.25,143.72,142.57,139.97,137.86,136.85,135.34,131.69,130.51,130.15,12

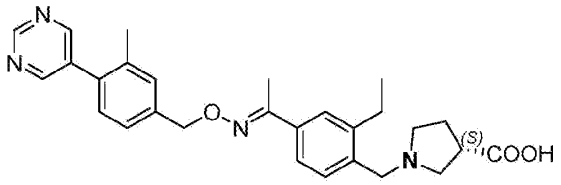
8.74,126.66,125.53,123.98,110.90,75.65,56.45,54.32,53.53,43.55,27.70,25.24,20.03,14.56,11.41.

[0300] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(吡啶-4-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物37)的结构



[0301] 淡黄色固体，产率19.2%。^{1}H NMR(600MHz,CD_3OD) δ 8.56(d,J=6.2Hz,2H),7.63(s,1H),7.56(d,J=8.1Hz,1H),7.47(d,J=8.1Hz,1H),7.40(d,J=6.2Hz,2H),7.37(s,1H),7.34(d,J=7.8Hz,1H),7.22(d,J=7.8Hz,1H),5.24(s,2H),4.42 - 4.33(m,2H),3.50(dd,J=11.2,5.7Hz,1H),3.38(d,J=7.8Hz,1H),3.34(s,1H),3.30 - 3.24(m,1H),3.11 - 3.04(m,1H),2.81(q,J=7.5Hz,2H),2.32(dd,J=15.2,7.1Hz,1H),2.28(s,3H),2.27(s,3H),2.22(dt,J=13.6,6.7Hz,1H),1.24(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.89,154.44,150.81,148.56,143.72,138.78,138.11,137.73,134.81,130.48,130.13,128.98,126.66,125.69,124.62,123.97,75.40,56.56,54.41,53.57,43.62,27.73,25.20,19.02,14.56,11.38.

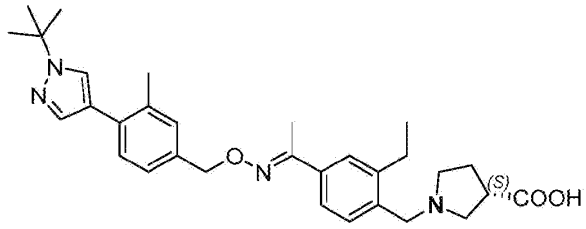
[0302] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(嘧啶-5-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物38)的结构



[0303] 淡黄色固体，产率19.7%。^{1}H NMR(600MHz,CD_3OD) δ 9.14(s,1H),8.78(s,2H),7.62(d,J=1.9Hz,1H),7.56(dd,J=8.1,1.9Hz,1H),7.47(d,J=8.1Hz,1H),7.40(d,J=1.7Hz,1H),7.37(dd,J=7.8,1.8Hz,1H),7.26(d,J=7.8Hz,1H),5.24(s,2H),4.42 - 4.32(m,2H),3.49(dd,J=11.2,5.8Hz,1H),3.38 - 3.32(m,2H),3.27(dt,J=10.8,7.3Hz,1H),3.08(ddd,J=14.4,8.7,5.8Hz,1H),2.81(q,J=7.5Hz,2H),2.35 - 2.31(m,1H),2.29(s,3H),2.27(s,3H),2.25 - 2.19(m,1H),1.24(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.06,156.57,156.36,1

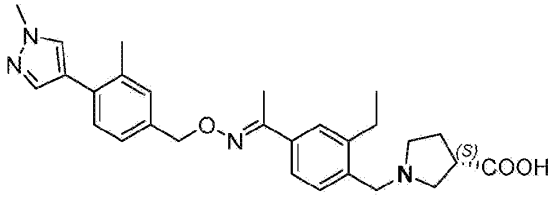
54.49,143.72,139.33,137.69,135.64,135.61,133.41,130.46,130.18,129.63,126.65,125.90,123.96,75.31,56.55,54.46,53.59,43.61,27.73,25.24,18.95,14.55,11.39.

[0304] (S,E)-1-(2-乙基-4-(1-((4-(-1-(叔丁基)-1H-吡唑-4-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物39)的结构



[0305] 淡黄色固体，产率31.1%。^{1}H NMR(600MHz,CD_3OD) δ 7.85(d,J=0.8Hz,1H),7.65 - 7.61(m,2H),7.56(dd,J=8.1,1.9Hz,1H),7.45(d,J=8.1Hz,1H),7.33(d,J=7.8Hz,1H),7.29 - 7.26(m,1H),7.23(dd,J=7.8,1.8Hz,1H),5.18(s,2H),4.39 - 4.31(m,2H),3.47(dd,J=11.1,5.8Hz,1H),3.33(dd,J=10.8,6.1Hz,2H),3.25(d,J=10.3Hz,1H),3.07(ddd,J=14.7,8.8,5.9Hz,1H),2.80(q,J=7.5Hz,2H),2.39(s,3H),2.33 - 2.26(m,1H),2.25(s,3H),2.24 - 2.19(m,1H),1.62(s,9H),1.24(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.15,154.25,143.67,137.80,137.77,136.36,134.87,131.84,130.41,130.20,128.69,126.65,125.63,125.41,123.95,121.12,75.70,58.41,56.64,54.55,53.60,43.65,28.66,27.75,25.19,20.06,14.54,11.39.MS(ESI)(m/z):$[M+H]^+$517.30.

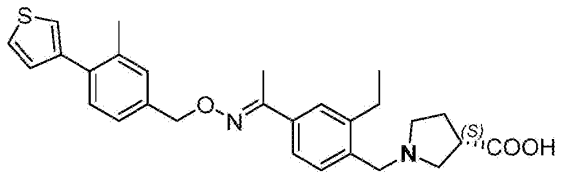
[0306] (S,E)-1-(2-乙基-4-(1-((3-甲基-4-(1-甲基-1H-吡唑-4-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物40)的结构



[0307] 淡黄色固体，产率29.5%。^{1}H NMR(600MHz,CD_3OD) δ 7.74(s,1H),7.62(d,J=1.9Hz,1H),7.61 - 7.60(m,1H),7.56(dd,J=8.1,1.9Hz,1H),7.45(d,J=8.1Hz,1H),7.32(d,J=7.8Hz,1H),7.28(d,J=1.8Hz,1H),7.22(dd,J=7.9,1.8Hz,1H),5.18(s,2H),4.41 - 4.32(m,2H),3.93(s,3H),3.49(dd,J=11.2,5.8Hz,1H),3.35(dd,J=11.2,7.0Hz,2H),3.26(dt,J=10.8,

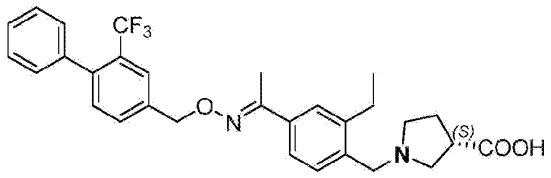
7.3Hz,1H),3.12－3.02(m,1H),2.80(q,J＝7.5Hz,2H),2.38(s,3H),2.30(ddd,J＝15.7,8.4,6.2Hz,1H),2.25(s,3H),2.24－2.18(m,1H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.95,154.26,143.69,138.10,137.85,136.50,134.86,131.45,130.44,130.23,129.63,128.60,126.66,125.64,123.96,121.92,75.66,56.60,54.49,53.58,43.61,37.44,27.73,25.22,20.08,14.53,11.38.MS(ESI)(m/z):$[M+H]^+$475.30.

[0308] (S,E)－1－(2－乙基－4－(1－(((3－甲基－4－(噻吩－3－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物41)的结构



[0309] 淡黄色固体，产率9.5%。^{1}H NMR(600MHz,CD_3OD) δ 7.63(d,J＝1.9Hz,1H),7.56(dd,J＝8.1,1.9Hz,1H),7.48－7.46(m,1H),7.43(dd,J＝4.9,3.0Hz,1H),7.29－7.27(m,1H),7.27(dd,J＝3.0,1.3Hz,1H),7.26－7.22(m,2H),7.13(dd,J＝5.0,1.3Hz,1H),5.19(s,2H),4.38(dd,J＝6.1,3.1Hz,2H),3.53－3.49(m,1H),3.36(dd,J＝10.8,4.3Hz,2H),3.28(dd,J＝10.9,7.2Hz,1H),3.09(td,J＝8.6,4.2Hz,1H),2.81－2.78(m,2H),2.31(s,4H),2.25(s,3H),2.24－2.20(m,1H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.04,154.24,143.72,141.88,137.88,137.04,136.10,135.31,130.50,129.99,129.30,128.45,126.68,125.40,124.71,123.99,122.26,75.67,56.42,54.43,53.60,43.54,27.71,25.26,19.58,14.56,11.41.

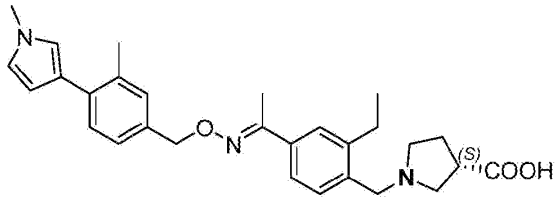
[0310] (S,E)－1－(2－乙基－4－(1－(((2－(三氟甲基)－[1,1'－联苯]－4－基)甲氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物42)的结构



[0311] 淡黄色固体，产率31.8%。^{1}H NMR(600MHz,CD_3OD) δ 7.81(s,1H),7.66(d,J＝7.8Hz,1H),7.63(d,J＝1.9Hz,1H),7.56(dd,J＝8.0,1.9Hz,1H),7.48(d,J＝8.1Hz,1H),7.38(dd,J＝5.1,1.9Hz,3H),7.34(d,J＝7.8Hz,1H),7.28(dd,J＝6.7,2.9Hz,2H),5.32(s,2H),4.41－4.32(m,2H),3.49(dd,J＝11.2,5.8Hz,1H),3.34(t,J＝8.1Hz,2H),3.29－3.23(m,1H),3.08(ddd,

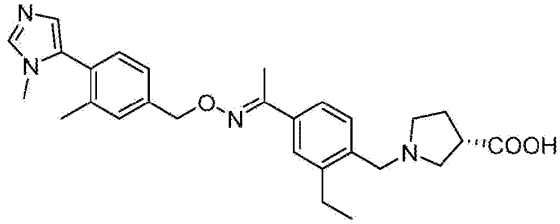
J＝14.4,8.7,5.9Hz,1H),2.81(q,J＝7.5Hz,2H),2.34－2.29(m,1H),2.29(s,3H),2.23(tt,J＝13.5,6.2Hz,1H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 179.63,154.93,143.74,140.81,139.60,138.23,137.55,132.04,130.96,130.48,128.64,128.62,127.45,127.36,126.66,125.35,125.31,123.97,74.69,56.58,54.49,53.60,43.68,27.75,25.23,14.52,11.41.MS(ESI)(m/z):$[M+H]^+$525.25.

[0312] (S,E)－1－(2－乙基－4－(1－((3－甲基－4－(1－甲基－1H－吡咯－3－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物43)的结构



[0313] 淡黄色固体，产率21.5％。^{1}H NMR(600MHz,CD_3OD) δ 7.61(s,1H),7.54(d,J＝7.8Hz,1H),7.44(d,J＝8.1Hz,1H),7.29(d,J＝8.0Hz,1H),7.20(s,1H),7.15(d,J＝7.8Hz,1H),6.74(s,1H),6.64(s,1H),6.21(s,1H),5.15(s,2H),4.35(t,J＝10.7Hz,2H),3.66(s,3H),3.48(dd,J＝11.3,5.7Hz,1H),3.34(s,2H),3.24(d,J＝9.9Hz,1H),3.07(d,J＝8.1Hz,1H),2.79(q,J＝7.5Hz,2H),2.39(s,3H),2.30－2.24(m,1H),2.23(s,3H),2.21(s,1H),1.23(t,J＝7.6Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.09,154.09,143.65,137.89,135.78,134.80,134.36,130.45,130.22,130.11,128.42,126.64,125.44,123.94,123.77,121.28,120.43,108.50,75.92,56.53,54.45,53.57,43.63,34.81,27.73,25.22,20.45,14.53,11.40.MS(ESI)(m/z):$[M+H]^+$474.25.

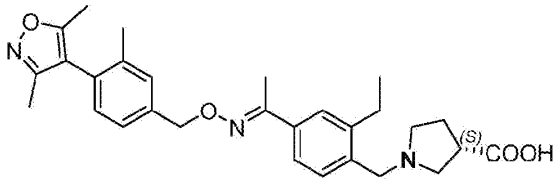
[0314] (S,E)－1－(2－乙基－4－(1－((3－甲基－4－(1－甲基－1H－咪唑－5－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物44)的结构



[0315] 淡黄色固体，产率27.1％。^{1}H NMR(600MHz,CD_3OD) δ 7.72(s,1H),7.62(s,1H),7.56(d,J＝7.9Hz,1H),7.46(d,J＝8.1Hz,1H),7.38(s,1H),7.32(d,J＝7.8Hz,1H),7.21(d,J＝7.8

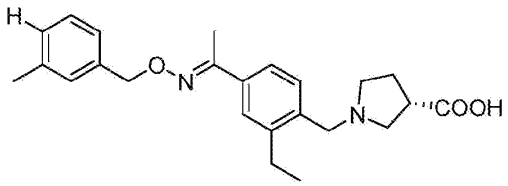
Hz,1H),6.88(s,1H),5.24(s,2H),4.34(d,J＝4.2Hz,2H),3.45(s,4H),3.34(s,2H),3.26(s,1H),3.07(q,J＝6.0Hz,1H),2.81(q,J＝7.6Hz,2H),2.27(s,3H),2.23(t,J＝6.7Hz,2H),2.18(s,3H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.17,154.52,143.68,139.34,138.14,137.90,137.62,132.16,130.91,130.41,129.62,128.07,126.63,126.33,125.24,123.94,75.41,56.69,54.56,53.60,43.72,30.75,27.78,25.23,18.73,14.54,11.42.MS(ESI)(m/z):$[M+H]^+$ 475.25.

[0316] (S,E)-1-(2-乙基-4-(1-(((3,5-二甲基异恶唑-4-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物45)的结构



[0317] 淡黄色固体，产率20.7％。^{1}H NMR(600MHz,CD_3OD) δ 7.64(s,1H),7.57(d,J＝8.1Hz,1H),7.48(d,J＝8.1Hz,1H),7.39(s,1H),7.31(d,J＝7.8Hz,1H),7.12(dd,J＝7.8,4.1Hz,1H),5.23(s,2H),4.40(d,J＝13.6Hz,2H),3.50(dd,J＝11.3,5.8Hz,1H),3.36(q,J＝10.0,9.1Hz,2H),3.30 - 3.25(m,1H),3.12 - 3.05(m,1H),2.82(q,J＝7.5Hz,2H),2.31(dd,J＝14.6,6.8Hz,1H),2.27(s,3H),2.26 - 2.23(m,1H),2.21(s,3H),2.14(s,3H),2.05(s,3H),1.25(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.08,165.70,159.25,154.41,143.72,138.64,137.45,130.52,130.46,129.72,128.36,126.66,125.58,123.98,115.90,75.51,56.54,54.47,53.59,43.60,27.73,25.24,18.47,14.55,11.43,9.83,8.99.MS(ESI)(m/z):$[M+H]^+$490.30.

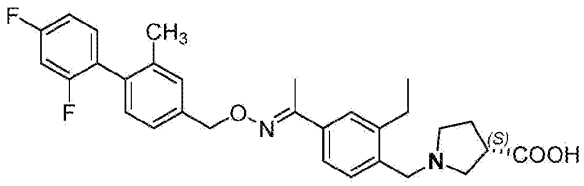
[0318] (S,E)-1-(2-乙基-4-(1-(((3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物46)的结构



[0319] 淡黄色固体，产率50.1％。^{1}H NMR(600MHz,CD_3OD) δ 7.62(d,J＝1.9Hz,1H),7.55(dd,J＝8.1,1.9Hz,1H),7.47(d,J＝8.1Hz,1H),7.25 - 7.19(m,2H),7.17(d,J＝7.5Hz,1H),7.

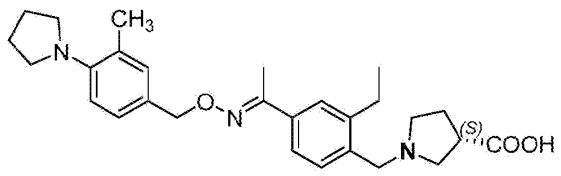
10(d,J＝7.5Hz,1H),5.16(s,2H),4.42－4.32(m,2H),3.50(dd,J＝11.3,5.9Hz,1H),3.38－3.33(m,2H),3.28(dd,J＝10.9,7.5Hz,1H),3.09(ddd,J＝14.6,8.5,5.8Hz,1H),2.81(q,J＝7.5Hz,2H),2.33(s,3H),2.32－2.28(m,1H),2.24(s,4H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.42,154.23,143.69,137.94,137.83,137.66,130.47,128.47,128.09,127.88,126.65,124.91,123.96,75.94,56.52,54.52,53.64,43.66,27.75,25.25,20.06,14.55,11.40.MS(ESI)(m/z):[M+H]$^+$395.25.

[0320] (S,E)－1－(2－乙基－4－(1－(((2',4'－二氟－2－甲基－[1,1'－联苯]－4－基)甲氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物47)的结构



[0321] 淡黄色固体，产率19.0％。^{1}H NMR(600MHz,CD_3OD) δ 7.63(s,1H),7.56(d,J＝7.9Hz,1H),7.47(d,J＝8.1Hz,1H),7.33(s,1H),7.28(d,J＝8.0Hz,1H),7.25(d,J＝7.5Hz,1H),7.14(d,J＝7.9Hz,1H),7.01(t,J＝8.8Hz,2H),5.22(s,2H),4.41－4.28(m,2H),3.48(dd,J＝11.1,5.7Hz,1H),3.37－3.32(m,2H),3.25(q,J＝8.0Hz,1H),3.07(t,J＝7.8Hz,1H),2.80(q,J＝7.5Hz,2H),2.34－2.28(m,1H),2.26(s,3H),2.22(d,J＝14.8Hz,1H),2.15(s,3H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 177.31,162.53,160.90,159.67,158.03,153.59,142.87,137.32,136.91,135.57,133.46,131.48,131.44,129.64,129.00,128.62,125.84,124.47,123.14,110.15,109.98,102.59,102.42,102.24,74.75,55.85,53.67,52.76,42.92,26.96,24.42,17.83,13.73,10.62.MS(ESI)(m/z):[M+H]$^+$507.25.

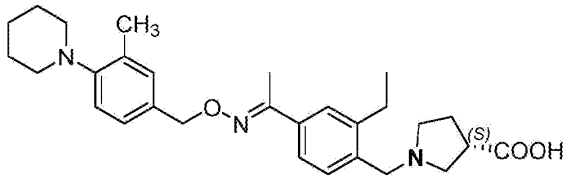
[0322] (S,E)－1－(2－乙基－4－(1－(((3－甲基－4－(吡咯烷－1－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物48)的结构



[0323] 淡黄色固体，产率17.5％。^{1}H NMR(600MHz,CD_3OD) δ 7.61(d,J＝1.9Hz,1H),7.54(dd,J＝8.0,1.9Hz,1H),7.46(d,J＝8.1Hz,1H),7.14(d,J＝2.1Hz,1H),7.11(dd,J＝8.2,2.2

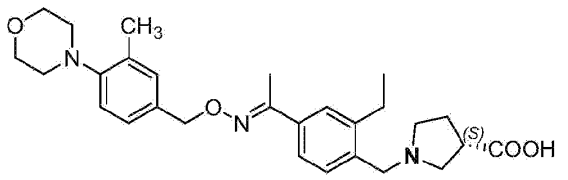
Hz,1H),6.87(d,J＝8.2Hz,1H),5.08(s,2H),4.36(d,J＝8.0Hz,2H),3.50(dd,J＝11.2,5.7Hz,1H),3.38－3.32(m,2H),3.26(dt,J＝10.9,7.3Hz,1H),3.15－3.10(m,4H),3.07(td,J＝8.8,4.4Hz,1H),2.80(q,J＝7.5Hz,2H),2.33－2.30(m,1H),2.29(s,3H),2.26－2.22(m,1H),2.20(s,3H),1.94－1.88(m,4H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.01,153.87,149.09,143.66,137.93,131.74,130.47,129.79,128.56,126.61,126.49,123.93,115.53,75.99,56.52,54.41,53.55,50.82,43.67,27.75,25.24,24.30,19.25,14.57,11.40.MS(ESI)(m/z):[M+H]$^+$464.30.

[0324] (S,E)－1－(2－乙基－4－(1－(((3－甲基－4－(哌啶－1－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物49)的结构



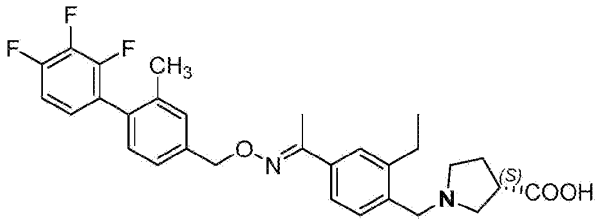
[0325] 淡黄色固体，产率19.4％。^{1}H NMR(500MHz,CD_3OD) δ 7.62(d,J＝1.9Hz,1H),7.55(dd,J＝8.1,1.9Hz,1H),7.47(d,J＝8.1Hz,1H),7.20(d,J＝2.1Hz,1H),7.17(dd,J＝8.1,2.1Hz,1H),6.99(d,J＝8.1Hz,1H),5.11(s,2H),4.39－4.29(m,2H),3.48(dd,J＝11.1,5.8Hz,1H),3.37(s,1H),3.35－3.31(m,1H),3.29－3.22(m,1H),3.12－3.04(m,1H),2.86－2.77(m,6H),2.32(dd,J＝13.2,7.4Hz,1H),2.29(s,3H),2.25(d,J＝12.9Hz,1H),2.23(s,3H),1.72(p,J＝5.7Hz,4H),1.59(q,J＝5.8,5.4Hz,2H),1.25(t,J＝7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.42,154.03,152.53,143.62,137.78,132.13,132.04,130.84,130.42,126.59,126.44,123.91,118.45,75.89,56.59,54.54,53.60,53.20,43.76,27.78,26.29,25.24,24.08,16.69,14.55,11.42.MS(ESI)(m/z):[M+H]$^+$478.30.

[0326] (S,E)－1－(2－乙基－4－(1－(((3－甲基－4－吗啉基苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物50)的结构



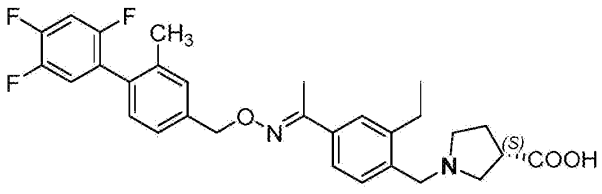
[0327] 淡黄色固体，产率20.7％。^{1}H NMR(500MHz,CD_3OD) δ 7.64(d,J＝1.8Hz,1H),7.57(dd,J＝8.1,1.9Hz,1H),7.48(d,J＝8.1Hz,1H),7.26－7.18(m,2H),7.04(dt,J＝8.1,1.9Hz,1H),5.13(s,2H),4.43－4.33(m,2H),3.88－3.77(m,4H),3.55－3.47(m,1H),3.37(dd,J＝9.5,6.3Hz,2H),3.32－3.26(m,1H),3.12(tt,J＝8.7,6.0Hz,1H),2.88(dq,J＝4.8,2.6Hz,4H),2.82(q,J＝7.6Hz,2H),2.39－2.29(m,4H),2.28－2.20(m,4H),1.29－1.23(m,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.88,154.10,151.00,143.69,137.88,132.82,132.22,130.99,130.47,130.17,126.64,126.57,123.96,118.46,75.76,67.06,56.48,54.55,53.67,52.11,43.64,27.74,25.25,16.72,14.56,11.41.MS(ESI)(m/z):$[M+H]^+$480.30.

[0328] (S,E)－1－(2－乙基－4－(1－(((2'，3'，4'－三氟－[1,1'－联苯]－4－基)甲氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物51)的结构



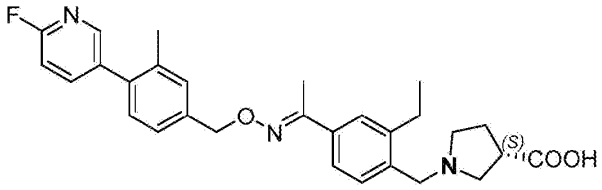
[0329] 淡黄色固体，产率20.1％。^{1}H NMR(600MHz,CD_3OD) δ 7.63(s,1H),7.56(d,J＝8.0Hz,1H),7.48(d,J＝8.2Hz,1H),7.34(s,1H),7.30(d,J＝7.9Hz,1H),7.16(d,J＝7.5Hz,2H),7.03(q,J＝6.3Hz,1H),5.22(s,2H),4.38(t,J＝10.0Hz,2H),3.50(s,1H),3.36(d,J＝8.6Hz,2H),3.28(d,J＝10.5Hz,1H),3.09(s,1H),2.80(q,J＝7.5Hz,2H),2.26(s,5H),2.16(s,3H),1.24(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 154.43,143.70,138.70,137.73,136.31,133.12,133.11,130.48,130.25,129.75,129.50,126.65,125.36,125.14,125.12,125.06,123.96,111.81,111.76,111.76,75.44,56.57,56.51,56.48,54.74,54.43,53.59,53.01,43.63,43.61,43.56,43.45,43.30,43.11,27.74,25.24,18.57,18.55,14.53,11.42.MS(ESI)(m/z):$[M+H]^+$525.20.

[0330] (S,E)－1－(2－乙基－4－(1－(((2'，4'，5'－三氟－2－甲基－[1,1'－联苯]－4－基)甲氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物52)的结构



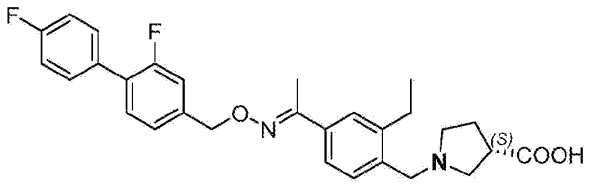
[0331] 淡黄色固体，产率17.9%。^{1}H NMR(600MHz,CD_3OD) δ 7.62(s,1H),7.55(d,J＝8.0 Hz,1H),7.51(d,J＝8.3Hz,1H),7.33(s,1H),7.28(d,J＝7.6Hz,1H),7.22(d,J＝6.7Hz,1H),7.14(d,J＝7.3Hz,2H),5.21(s,2H),4.38(t,J＝8.9Hz,2H),3.49(s,1H),3.35(s,2H),3.29(s,1H),3.10(s,1H),2.81(d,J＝7.5Hz,2H),2.30(d,J＝7.4Hz,1H),2.25(s,3H),2.23(s,1H),2.16(s,3H),1.23(t,J＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 155.58,154.43,153.96,150.21,148.51,147.31,145.70,143.71,138.63,137.70,136.34,133.18,130.53,130.33,129.70,129.49,126.64,125.34,123.95,118.93,118.76,105.40,105.26,105.20,105.06,75.46,56.40,54.49,53.66,43.71,27.79,25.30,18.59,18.57,14.56,11.43.MS(ESI)(m/z):$[M+H]^+$525.25.

[0332] (S,E)−1−(2−乙基−4−(1−(((4−(6−氟吡啶−3−基)−3−甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷−3−羧酸(化合物53)的结构



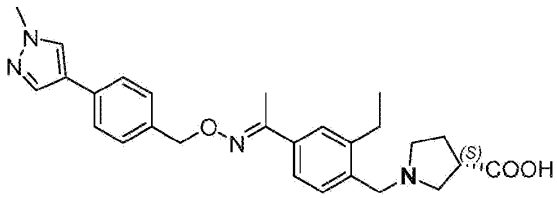
[0333] 淡黄色固体，产率25.7%。^{1}H NMR(500MHz,CD_3OD) δ 8.12 - 8.08(m,1H),7.88(ddd,J＝8.5,7.8,2.6Hz,1H),7.62(d,J＝1.9Hz,1H),7.55(dd,J＝8.0,1.9Hz,1H),7.47(d,J＝8.1Hz,1H),7.35(d,J＝1.7Hz,1H),7.31(dd,J＝7.8,1.8Hz,1H),7.19(d,J＝7.8Hz,1H),7.11(ddd,J＝8.5,2.6,0.7Hz,1H),5.22(s,2H),4.39 - 4.31(m,2H),3.48(dd,J＝11.2,5.7Hz,1H),3.36(s,1H),3.33(d,J＝2.6Hz,1H),3.29 - 3.21(m,1H),3.08(tt,J＝8.5,5.8Hz,1H),2.80(q,J ＝7.5 Hz,2H),2.34 - 2.27(m,1H),2.25(s,3H),2.24(s,3H),2.21(dd,J＝13.5,6.4Hz,1H),1.23(t,J＝7.6Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 179.54,165.00,163.11,155.80,148.23,148.12,145.08,143.92,143.86,139.83,139.04,137.56,136.94,136.90,136.84,131.85,131.43,130.95,128.01,127.07,125.32,110.23,109.93,76.82,57.91,55.84,54.97,45.08,29.14,26.63,20.46,15.94,12.80.MS(ESI)(m/z):$[M+H]^+$490.25.

[0334] (S,E)−1−(2−乙基−4−(1−(((2,4'−二氟−[1,1'−联苯]−4−基)甲氧基)亚氨基)乙基)苄基)吡咯烷−3−羧酸(化合物54)的结构



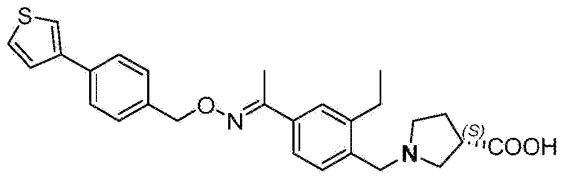
[0335] 淡黄色固体，产率28.1％。^{1}H NMR(600MHz,CD_3OD) δ 7.62(s,1H),7.56(s,2H),7.52(ddJ＝7.3,5.3Hz,2H),7.42(tJ＝8.0Hz,1H),7.27(dJ＝7.9Hz,1H),7.21(dJ＝11.6Hz,1H),7.15(tJ＝8.8Hz,2H),5.24(s,2H),4.46－4.38(m,2H),3.54(ddJ＝11.3,6.2Hz,1H),3.44－3.37(m,2H),3.36(s,1H),3.16－3.10(m,1H),2.82(qJ＝7.5Hz,2H),2.34(ddJ＝14.3,7.3Hz,1H),2.28(s,3H),2.27－2.23(m,1H),1.23(tJ＝7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 179.36,163.26,161.63,160.25,158.62,154.74,143.80,140.37,137.67,131.67,130.67,130.55,130.53,130.49,130.47,130.32,130.29,130.06 127.05,126.67,123.98,123.75,123.72,115.11,114.95,114.81,74.67,56.19,54.41,53.74,43.59,27.72,25.37,14.56,11.43.MS(ESI)(m/z):$[M+H]^+$493.25.

[0336] (S,E)－1－(2－乙基－4－(1－((4－(1－甲基－1H－吡唑－4－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物55)的结构



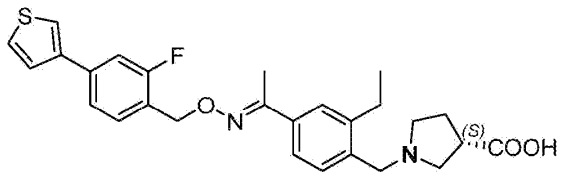
[0337] 淡黄色固体，产率34.3％。^{1}H NMR(500MHz,CD_3OD) δ 7.94－7.88(m,1H),7.79(ddJ＝2.7,1.2Hz,1H),7.62(qJ＝1.8Hz,1H),7.56(dtJ＝8.1,2.2Hz,1H),7.52(dtJ＝8.3,2.0Hz,2H),7.45(dJ＝8.1Hz,1H),7.39(ddJ＝8.2,1.9Hz,2H),5.20(s,2H),4.43－4.33(m,2H),3.92－3.87(m,3H),3.52(ddJ＝11.3,5.7Hz,1H),3.37(dtJ＝10.6,7.1Hz,2H),3.28(dJ＝9.4Hz,1H),3.14－3.05(m,1H),2.79(dttJ＝7.6,3.9,2.0Hz,2H),2.31(dtJ＝15.7,7.4Hz,1H),2.26－2.24(m,3H),2.22(ddJ＝13.7,6.9Hz,1H),1.25－1.22(m,3H).^{13}C NMR(126MHz,CD_3OD) δ 177.66,154.30,143.73,137.91,136.13,135.97,132.02,130.48,129.94,128.49,127.75,126.69,124.90,123.99,122.83,75.65,56.45,54.38,53.56,43.44,37.53,27.67,25.22,14.54,11.39.MS(ESI)(m/z):$[M+H]^+$461.30.

[0338] (S,E)-1-(2-乙基-4-(1-((4-(噻吩-3-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物56)的结构



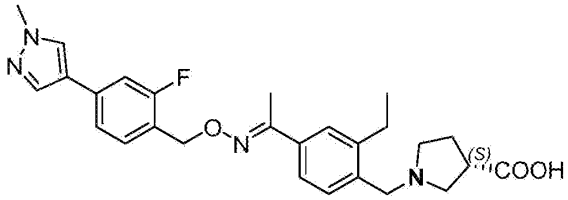
[0339] 淡黄色固体，产率19.7%。^{1}H NMR(500MHz,CD_3OD) δ 7.64(dd,J=8.5,2.0Hz,3H),7.61(dd,J=2.8,1.5Hz,1H),7.58(dd,J=8.1,1.9Hz,1H),7.48 - 7.40(m,5H),5.23(s,2H),4.40(d,J=2.5Hz,2H),3.53(dd,J=11.3,5.8Hz,1H),3.37(dd,J=12.5,5.6Hz,2H),3.27(d,J=10.5Hz,1H),3.10(ddd,J=11.8,8.6,5.7Hz,1H),2.81(q,J=7.5Hz,2H),2.32(dq,J=15.8,7.9Hz,1H),2.27(s,3H),2.22(dd,J=13.4,6.7Hz,1H),1.25(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 154.35,143.75,141.83,137.95,136.87,135.39,130.47,128.38,126.72,125.90,125.85,125.71,124.02,119.91,75.59,56.53,54.43,53.55,43.44,27.68,25.21,14.53,11.39.MS(ESI)(m/z):$[M+H]^+$463.20

[0340] (S,E)-1-(2-乙基-4-(1-((2-氟-4-(噻吩-3-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物57)的结构



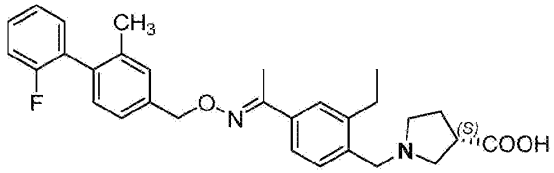
[0341] 淡黄色固体，产率27.7%。^{1}H NMR(500MHz,CD_3OD) δ 7.67(dd,J=2.9,1.4Hz,1H),7.63(d,J=2.0Hz,1H),7.56(dd,J=8.1,1.9Hz,1H),7.51 - 7.45(m,4H),7.44(dd,J=5.1,1.4Hz,1H),7.40(dd,J=11.4,1.6Hz,1H),5.28(d,J=1.1Hz,2H),4.43 - 4.34(m,2H),3.53(dd,J=11.3,5.6Hz,1H),3.43 - 3.34(m,2H),3.28(dt,J=11.0,7.4Hz,1H),3.15 - 3.05(m,1H),2.80(q,J=7.5Hz,2H),2.37 - 2.29(m,1H),2.28 - 2.19(m,4H),1.24(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 177.72,162.31,160.35,154.57,143.71,140.56,137.91,137.84,137.72,131.06,130.50,130.02,126.66,126.26,125.60,123.97,123.49,123.37,121.53,121.51,121.01,112.54,112.35,69.22,69.19,56.44,54.29,53.52,43.54,27.69,25.22,14.51,11.30.MS(ESI)(m/z):$[M+H]^+$481.20.

[0342] (S,E)-1-(2-乙基-4-(1-((2-氟-4-(1-甲基-1H-吡唑-4-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物58)的结构



[0343] 淡黄色固体，产率31.6%。^{1}H NMR(500MHz,CD_3OD) δ 8.00 – 7.93(m,1H),7.82(d,J=0.8Hz,1H),7.63(d,J=2.0Hz,1H),7.56(dd,J=8.1,1.9Hz,1H),7.50 – 7.41(m,2H),7.34(dd,J=7.8,1.7Hz,1H),7.30(dd,J=11.3,1.7Hz,1H),5.26(s,2H),4.44 – 4.34(m,2H),3.91(s,3H),3.53(dd,J=11.2,5.7Hz,1H),3.43 – 3.34(m,2H),3.28(dt,J=11.0,7.4Hz,1H),3.10(tt,J=8.7,5.7Hz,1H),2.81(q,J=7.6Hz,2H),2.37 – 2.29(m,1H),2.25(s,4H),1.25(t,J=7.6Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 177.73,162.41,160.45,154.51,143.71,137.73,136.16,134.81,134.74,131.22,131.18,130.49,130.06,128.17,126.65,123.95,122.64,122.52,121.79,121.77,120.55,120.52,111.53,111.35,69.24,69.22,56.48,54.31,53.53,43.56,37.61,27.69,25.21,14.50,11.28MS(ESI)(m/z):$[M+H]^+$479.30.

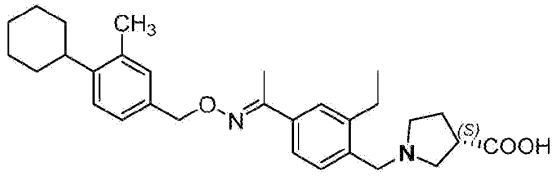
[0344] (S,E)-1-(2-乙基-4-(1-(((2'-氟-2-甲基-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物59)的结构



[0345] 淡黄色固体，产率33.5%。^{1}H NMR(500MHz,CD_3OD) δ 7.63(s,1H),7.56(d,J=8.0Hz,1H),7.49(d,J=8.1Hz,1H),7.38(td,J=8.9,8.2,3.6Hz,1H),7.32(s,1H),7.28(d,J=7.7Hz,1H),7.22(d,J=4.6Hz,2H),7.15(t,J=8.0Hz,2H),5.22(s,2H),4.38 – 4.31(m,2H),3.48(dd,J=11.3,6.1Hz,1H),3.35(s,2H),3.29 – 3.24(m,1H),3.09(ddd,J=14.7,8.6,6.1Hz,1H),2.81(q,J=7.5Hz,2H),2.31(dd,J=14.5,7.0Hz,1H),2.27(s,3H),2.23(dd,J=13.4,6.8Hz,1H),2.16(s,3H),1.24(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 179.07,160.43,158.81,154.38,143.68,137.85,137.75,136.26,135.28,131.31,131.28,130.47,129.67,129.35,129.09,1

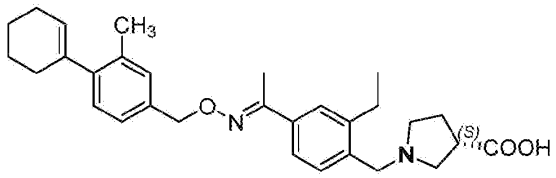
29.04,128.96,126.66,125.19,123.95,123.92,123.89,115.08,114.93,75.63,56.46,54.60,53.70,43.65,27.75,25.28,18.68,14.54,11.44.MS(ESI)(m/z):$[M+H]^+$489.25.

[0346] (S,E)-1-(2-乙基-4-(1-(((4-环己基-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物60)的结构



[0347] 淡黄色固体，产率34.5%。^{1}H NMR(500MHz,CD_3OD) δ 7.62(d,J=2.0Hz,1H),7.55(dd,J=8.1,1.9Hz,1H),7.48(d,J=8.1Hz,1H),7.20 - 7.13(m,3H),5.13(s,2H),4.42 - 4.30(m,2H),3.50(dd,J=11.2,5.8Hz,1H),3.36(dd,J=11.7,7.9Hz,2H),3.27(dt,J=10.9,7.3Hz,1H),3.09(ddd,J=14.6,8.9,5.8Hz,1H),2.81(q,J=7.5Hz,2H),2.74(ddd,J=11.5,9.7,3.2Hz,1H),2.32(s,4H),2.23(s,4H),1.91 - 1.82(m,2H),1.81 - 1.73(m,3H),1.52 - 1.39(m,4H),1.33 - 1.28(m,1H),1.25(t,J=7.6Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.14,154.05,145.25,143.65,137.82,134.85,134.63,130.45,130.24,129.88,126.62,125.87,124.97,123.93,75.90,56.52,54.43,53.57,43.69,39.82,33.49,27.76,26.83,26.02,25.24,18.11,14.56,11.42.MS(ESI)(m/z):$[M+H]^+$477.30.

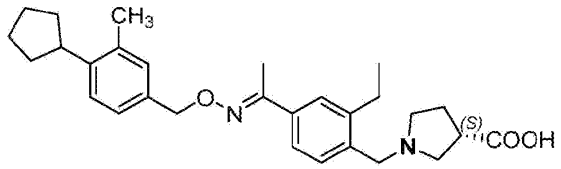
[0348] (S,E)-1-(2-乙基-4-(1-((2-甲基-2',3',4',5'-四氢-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物61)的结构



[0349] 淡黄色固体，产率31.2%。^{1}H NMR(500MHz,CD_3OD) δ 7.60(d,J=2.0Hz,1H),7.52(dd,J=8.1,1.9Hz,1H),7.46(d,J=8.1Hz,1H),7.15(d,J=1.7Hz,1H),7.11(dd,J=7.8,1.8Hz,1H),6.97(d,J=7.7Hz,1H),5.47(td,J=3.8,2.0Hz,1H),5.11(s,2H),4.39 - 4.28(m,2H),3.47(dd,J=11.1,5.7Hz,1H),3.37 - 3.31(m,2H),3.24(dt,J=10.9,7.3Hz,1H),3.06(tt,J=8.9,5.8Hz,1H),2.78(q,J=7.5Hz,2H),2.33 - 2.21(m,5H),2.20(s,3H),2.16 - 2.10(m,4H),1.73(tdd,J=8.2,4.9,2.6Hz,2H),1.67(qq,J=5.8,2.6Hz,2H),1.22(t,J=7.5Hz,3H).^{13}C NMR(126

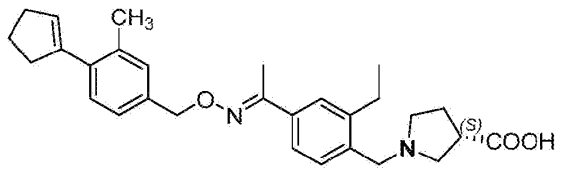
MHz,CD_3OD) δ 178.11,154.10,144.02,143.65,138.75,137.74,135.99,134.52,130.49,130.29,129.59,127.88,126.60,125.31,125.22,123.93,75.85,56.47,54.35,53.53,43.72,29.82,27.78,25.26,24.97,22.81,21.92,18.61,14.59,11.45.MS(ESI)(m/z):$[M+H]^+$475.30

[0350] (S,E)-1-(2-乙基-4-(1-(((4-环戊基-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物62)的结构



[0351] 淡黄色固体，产率33.5％。^1H NMR(500MHz,CD_3OD) δ 7.61(d,J＝1.9Hz,1H),7.54(dd,J＝8.0,1.9Hz,1H),7.47(d,J＝8.1Hz,1H),7.19(d,J＝7.8Hz,1H),7.16(d,J＝1.9Hz,1H),7.13(d,J＝1.8Hz,1H),5.11(s,2H),4.45 - 4.30(m,2H),3.52(dd,J＝11.3,5.8Hz,1H),3.41 - 3.32(m,2H),3.28(dd,J＝11.0,7.4Hz,1H),3.19(tt,J＝9.2,7.5Hz,1H),3.09(ddd,J＝14.6,8.8,5.8Hz,1H),2.79(q,J＝7.6Hz,2H),2.31(s,4H),2.21(s,4H),1.99(ddddd,J＝12.2,10.9,6.7,2.8,1.4Hz,2H),1.85 - 1.76(m,2H),1.72 - 1.64(m,2H),1.58 - 1.47(m,2H),1.23(t,J＝7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.02,154.03,143.86,143.70,137.92,135.45,134.86,130.52,129.89,129.76,126.65,125.83,124.80,123.98,75.90,56.35,54.35,53.58,43.56,41.31,33.26,27.72,25.27,25.10,18.61,14.59,11.43.MS(ESI)(m/z):$[M+H]^+$463.30

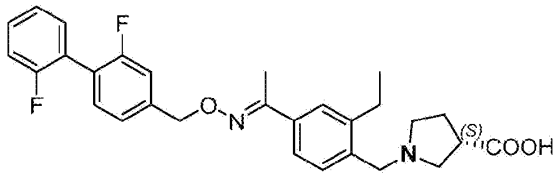
[0352] (S,E)-1-(2-乙基-4-(1-((4-(环戊-1-烯-1-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物63)的结构



[0353] 淡黄色固体，产率30.4％。^1H NMR(500MHz,CD_3OD) δ 7.60(d,J＝1.9Hz,1H),7.53(dd,J＝8.1,1.9Hz,1H),7.46(d,J＝8.1Hz,1H),7.18(d,J＝1.7Hz,1H),7.16 - 7.10(m,2H),5.73(p,J＝2.2Hz,1H),5.13(s,2H),4.39 - 4.26(m,2H),3.48(dd,J＝11.2,5.7Hz,1H),3.37 - 3.32(m,1H),3.29(s,1H),3.26 - 3.20(m,1H),3.06(ddd,J＝14.6,8.8,5.8Hz,1H),2.78(q,J＝7.5Hz,2H),2.67 - 2.58(m,2H),2.51(tq,J＝7.2,2.4Hz,2H),2.31(s,3H),2.30 - 2.19(m,5H),1.97

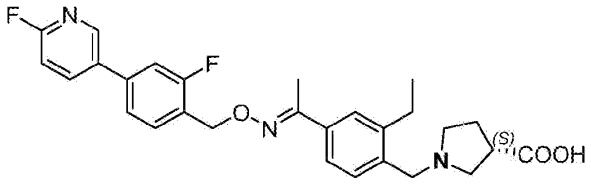
(p,J＝7.5Hz,2H),1.22(t,J＝7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.11,154.18,143.66,143.14,137.75,137.50,136.20,135.06,130.47,130.29,130.01,128.84,127.61,126.61,125.17,123.93,75.74,56.50,54.38,53.54,43.71,36.25,33.04,27.76,25.24,23.30,20.04,14.57,11.43.MS(ESI)(m/z):$[M+H]^+$461.30.

[0354] (S,E)-1-(2-乙基-4-(1-((2,2'-二氟-[1,1'-联苯]-4-基)甲氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物64)的结构



[0355] 淡黄色固体，产率28.9%。^{1}H NMR(500MHz,CD_3OD) δ 7.63(d,J＝1.9Hz,1H),7.57(dd,J＝8.1,2.0Hz,1H),7.47(d,J＝8.1Hz,1H),7.44 - 7.40(m,1H),7.39(d,J＝2.5Hz,1H),7.38(d,J＝2.6Hz,1H),7.31(dd,J＝7.9,1.6Hz,1H),7.28 - 7.25(m,1H),7.24(d,J＝1.7Hz,1H),7.19(ddd,J＝9.6,8.2,1.2Hz,1H),5.28(s,2H),4.31(d,J＝3.9Hz,2H),3.44(dd,J＝10.6,5.7Hz,1H),3.29(d,J＝9.8Hz,2H),3.23(s,1H),3.07(ddd,J＝14.5,8.6,6.0Hz,1H),2.81(q,J＝7.5Hz,2H),2.31(d,J＝0.8Hz,3H),2.29 - 2.25(m,1H),2.23(dd,J＝13.6,7.0Hz,1H),1.27 - 1.23(m,3H).^{13}C NMR(126MHz,CD_3OD) δ 160.79,160.67,158.83,154.90,143.63,141.17,141.11,137.38,131.32,131.22,130.37,129.77,129.71,126.62,123.99,123.96,123.90,123.32,123.30,123.15,122.70,122.57,115.27,115.10,114.64,114.46,74.66,56.68,54.68,53.65,43.80,27.79,25.22,14.50,11.45.MS(ESI)(m/z):$[M+H]^+$493.20.

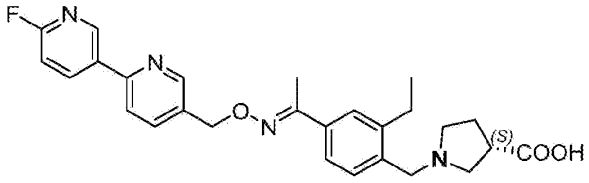
[0356] (S,E)-1-(2-乙基-4-(1-((2-氟-4-(6-氟吡啶-3-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物65)的结构



[0357] 淡黄色固体，产率20.3%。^{1}H NMR(500MHz,CD_3OD) δ 8.49 - 8.43(m,1H),8.23 - 8.16(m,1H),7.64(q,J＝1.8Hz,1H),7.61(dt,J＝7.8,1.8Hz,1H),7.58(dq,J＝9.9,1.9Hz,1

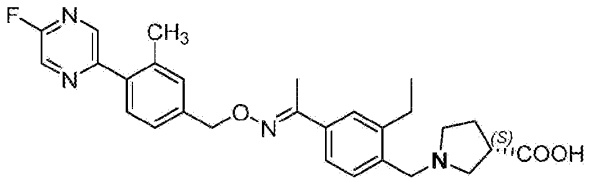
H),7.49(s,1H),7.47(d,J＝4.2Hz,1H),7.44(ddd,J＝10.5,3.9,2.0Hz,1H),7.16(dq,J＝8.5,2.4Hz,1H),5.34(d,J＝2.2Hz,2H),4.43－4.34(m,2H),3.52(dd,J＝11.2,5.8Hz,1H),3.41－3.37(m,1H),3.36－3.34(m,1H),3.28(dd,J＝10.9,7.3Hz,1H),3.10(tt,J＝8.9,5.8Hz,1H),2.85－2.78(m,2H),2.37－2.29(m,1H),2.27(q,J＝2.6,2.2Hz,3H),2.23(dd,J＝13.5,6.7Hz,1H),1.25(tt,J＝7.6,1.9Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 162.39,154.77,145.28,145.16,143.72,140.36,140.29,138.32,137.59,131.37,131.33,130.46,130.34,126.66,125.13,125.01,123.96,122.37,113.51,113.32,109.52,109.22,69.01,56.52,54.43,53.58,43.59,27.71,25.21,14.50,11.28.MS(ESI)(m/z):$[M+H]^+$494.20

[0358] (S,E)－1－(2－乙基－4－(1－(((6'－氟－[2,3'－联吡啶]－5－基)甲氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物66)的结构



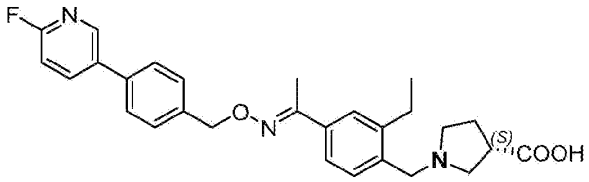
[0359] 淡黄色固体，产率17.2％。^{1}H NMR(500MHz,CD_3OD) δ 8.84－8.80(m,1H),8.72(dd,J＝2.3,0.9Hz,1H),8.54(ddd,J＝8.6,7.6,2.6Hz,1H),7.98(dd,J＝8.1,2.2Hz,1H),7.92(dd,J＝8.1,0.9Hz,1H),7.64(d,J＝2.0Hz,1H),7.58(dd,J＝8.1,1.9Hz,1H),7.49(d,J＝8.1Hz,1H),7.19(ddd,J＝8.6,2.6,0.6Hz,1H),5.33(s,2H),4.45－4.35(m,2H),3.53(dd,J＝11.2,5.7Hz,1H),3.42－3.37(m,1H),3.37－3.34(m,1H),3.29(dd,J＝11.0,7.3Hz,1H),3.11(ddt,J＝11.2,8.4,5.9Hz,1H),2.82(q,J＝7.5Hz,2H),2.34(dt,J＝15.1,7.7Hz,1H),2.29(s,3H),2.28－2.21(m,1H),1.25(t,J＝7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 177.73,164.91,162.99,155.08,152.89,149.35,145.86,145.74,143.78,140.31,140.25,137.56,137.50,133.65,132.98,132.94,130.50,130.31,126.69,123.99,120.45,109.42,109.12,72.79,56.49,54.38,53.57,43.52,27.69,25.22,14.53,11.38.MS(ESI)(m/z):$[M+H]^+$477.20.

[0360] (S,E)－1－(2－乙基－4－(1－(((4－(5－氟吡嗪－2－基)－3－甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物67)的结构



[0361] 淡黄色固体，产率16.3%。^{1}H NMR(500MHz,CD_3OD) δ 8.59(dd,J=8.3,1.4Hz,1H),8.38(d,J=1.6Hz,1H),7.66(d,J=1.9Hz,1H),7.60(dd,J=8.1,1.9Hz,1H),7.51(d,J=8.1Hz,1H),7.43(d,J=7.7Hz,1H),7.40(s,1H),7.38 - 7.35(m,1H),5.27(s,2H),4.49 - 4.41(m,2H),3.58(dd,J=11.4,6.0Hz,1H),3.45(d,J=8.2Hz,1H),3.41(d,J=7.7Hz,1H),3.39 - 3.34(m,1H),3.20 - 3.12(m,1H),2.83(q,J=7.5Hz,2H),2.38(s,3H),2.35(dd,J=9.1,6.9Hz,1H),2.30(s,3H),2.28 - 2.24(m,1H),1.29 - 1.25(m,3H).^{13}C NMR(126MHz,CD_3OD) δ 179.74,154.46,152.91,143.82,141.30,141.23,139.46,137.93,136.38,135.09,131.95,131.65,130.58,130.32,129.70,129.58,126.73,125.50,124.04,75.35,56.22,54.40,53.64,43.26,27.61,25.28,19.04,14.57,11.40.MS(ESI)(m/z):$[M+H]^+$491.25.

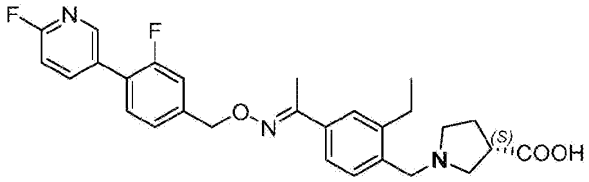
[0362] (S,E)-1-(2-乙基-4-(1-(((4-(6-氟吡啶-3-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物68)的结构



[0363] 淡黄色固体，产率27.6%。^{1}H NMR(500MHz,CD_3OD) δ 8.41(dt,J=2.7,0.8Hz,1H),8.16(ddd,J=8.5,7.6,2.6Hz,1H),7.63(d,J=1.9Hz,1H),7.62(d,J=1.8Hz,1H),7.61(d,J=2.0Hz,1H),7.57(dd,J=8.1,1.9Hz,1H),7.54(d,J=1.8Hz,1H),7.52(d,J=1.8Hz,1H),7.48(d,J=8.1Hz,1H),7.13(ddd,J=8.5,2.6,0.7Hz,1H),5.28(s,2H),4.43 - 4.34(m,2H),3.52(dd,J=11.2,5.7Hz,1H),3.37(ddd,J=11.0,8.0,3.1Hz,2H),3.29(dt,J=11.0,7.3Hz,1H),3.10(tt,J=8.5,5.7Hz,1H),2.81(q,J=7.5Hz,2H),2.38 - 2.30(m,1H),2.28(s,3H),2.24(dt,J=13.6,6.8Hz,1H),1.24(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 177.94,163.99,162.09,154.52,145.03,144.92,143.73,140.27,140.21,138.46,137.72,135.77,134.78,134.74,130.4

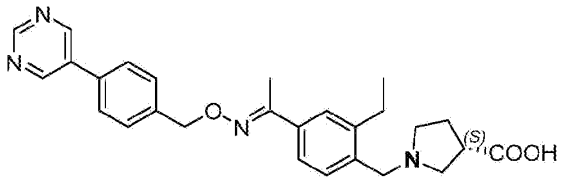
8,130.19,128.57,126.66,126.64,123.97,109.39,109.09,75.30,56.45,54.36,53.56,43.56,27.71,25.24,14.55,11.42.MS(ESI)(m/z):$[M+H]^+$476.20.

[0364] (S,E)-1-(2-乙基-4-(1-(((3-氟-4-(6-氟吡啶-3-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物69)的结构



[0365] 淡黄色固体，产率29.2%。^{1}H NMR(500MHz,CD_3OD) δ 8.39(s,1H),8.14(d,J=8.5Hz,1H),7.64(d,J=4.0Hz,1H),7.60 - 7.55(m,1H),7.53(dd,J=8.0,2.3Hz,1H),7.47(dd,J=8.2,2.1Hz,1H),7.38 - 7.33(m,1H),7.32(d,J=11.2Hz,1H),7.19(dd,J=8.9,2.9Hz,1H),5.29(d,J=4.3Hz,2H),4.41 - 4.30(m,2H),3.48(dd,J=10.8,5.4Hz,1H),3.37(s,1H),3.26(q,J=9.3,8.4Hz,2H),3.09(tt,J=8.5,5.9Hz,1H),2.83(q,J=5.8,4.4Hz,2H),2.34 - 2.22(m,5H),1.27 - 1.22(m,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.47,163.95,162.05,160.52,158.55,154.93,146.85,146.82,146.74,146.70,143.71,142.17,142.11,141.75,141.69,137.46,130.72,130.44,130.22,130.19,129.71,126.64,123.99,123.97,123.94,123.35,123.24,115.19,115.01,109.24,108.94,74.50,56.56,54.53,53.63,43.69,27.74,25.23,14.52,11.43..MS(ESI)(m/z):$[M+H]^+$494.20

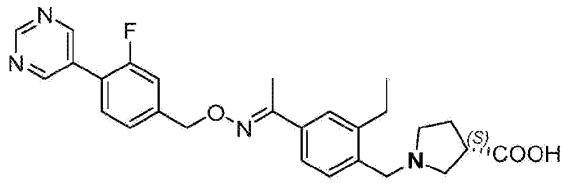
[0366] (S,E)-1-(2-乙基-4-(1-(((4-(嘧啶-5-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸的(化合物70)结构



[0367] 淡黄色固体，产率19.8%。^{1}H NMR(500MHz,CD_3OD) δ 9.17 - 9.12(m,1H),9.11 - 9.05(m,2H),7.75(dd,J=9.5,3.5Hz,2H),7.65 - 7.55(m,4H),7.47(d,J=8.1Hz,1H),5.32(d,J=4.0Hz,2H),4.33(s,2H),3.43(dd,J=10.8,6.1Hz,1H),3.31 - 3.20(m,3H),3.08(q,J=7.5,7.0Hz,1H),2.88 - 2.74(m,2H),2.31 - 2.29(m,3H),2.28 - 2.19(m,2H),1.25(ddd,J=9.6,

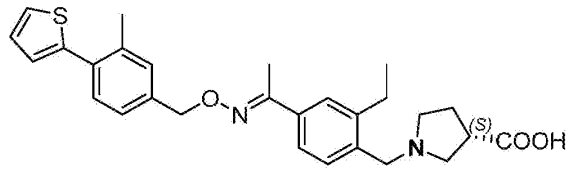
4.3,2.7Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.39,156.47,154.70,154.64,143.64,139.57,137.42,134.33,133.16,130.98,130.38,128.74,126.71,126.58,123.88,75.16,56.68,54.58,53.59,43.81,27.79,25.22,14.53,11.43.MS(ESI)(m/z):[M+H]$^+$459.20

[0368] (S,E)-1-(2-乙基-4-(1-(((3-氟-4-(嘧啶-5-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物71)的结构



[0369] 淡黄色固体，产率30.0%。^{1}H NMR(600MHz,CD_3OD) δ 9.39 – 9.24(m,1H),9.14(d,J=8.3Hz,2H),7.84 – 7.46(m,6H),5.45(d,J=7.7Hz,2H),4.58 – 4.42(m,2H),3.67 – 3.57(m,1H),3.53(s,1H),3.45(s,1H),3.39(d,J=9.6Hz,1H),3.28 – 3.19(m,1H),2.96(q,J=7.5Hz,2H),2.49 – 2.44(m,2H),2.42(d,J=2.3Hz,1H),2.37(q,J=6.8Hz,1H),1.40 – 1.37(m,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.30,160.69,158.72,156.78,156.20,156.16,155.06,143.69,142.91,142.85,137.34,130.42,130.09,130.07,129.97,129.95,126.61,124.22,124.20,123.92,120.82,120.71,115.26,115.07,74.40,56.66,54.53,53.59,43.77,27.77,25.22,14.52,11.43.MS(ESI)(m/z):[M+H]$^+$477.20

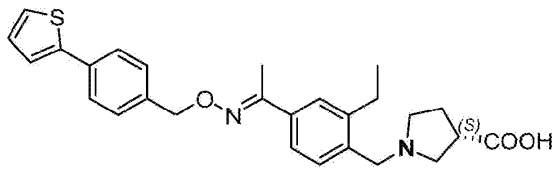
[0370] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(噻吩-2-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物72)的结构



[0371] 淡黄色固体，产率18.3%。^{1}H NMR(500MHz,CD_3OD) δ 7.62(s,1H),7.54(d,J=7.8Hz,1H),7.47(d,J=8.0Hz,1H),7.39(d,J=4.6Hz,1H),7.38 – 7.28(m,2H),7.23(d,J=7.8Hz,1H),7.14 – 7.01(m,2H),5.19(s,2H),4.34(d,J=6.8Hz,2H),3.48(dd,J=11.2,5.8Hz,1H),3.35(s,1H),3.31(s,1H),3.25(q,J=10.5,8.7Hz,1H),3.13 – 3.02(m,1H),2.79(q,J=7.3Hz,2H),2.37(s,3H),2.24(q,J=6.5Hz,5H),1.23(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.28,154.41,143.66,142.51,137.70,135.65,133.55,130.47,130.21,129.96,126.81,126.62,

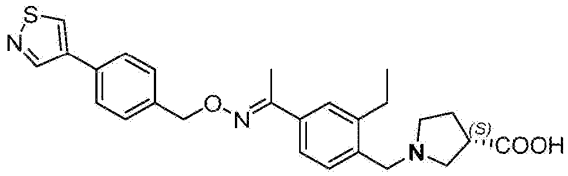
126.22,125.44,124.87,123.95,75.48,56.50,54.42,53.56,43.76,27.79,25.25,20.01,14.58,11.49.MS(ESI)(m/z):[M+H]$^+$477.20

[0372] (S,E)-1-(2-乙基-4-(1-((4-(噻吩-2-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸的(化合物73)结构



[0373] 淡黄色固体，产率21.2%。^{1}H NMR(500MHz,CD_3OD) δ 7.64 - 7.59(m,3H),7.56(dd,J=8.1,2.0Hz,1H),7.47(d,J=8.1Hz,1H),7.43 - 7.39(m,2H),7.36(ddd,J=8.2,4.4,1.2Hz,2H),7.08(dd,J=5.1,3.6Hz,1H),5.22(s,2H),4.40 - 4.30(m,2H),3.49(dd,J=11.2,5.8Hz,1H),3.35(d,J=7.7Hz,1H),3.32(s,1H),3.26(dt,J=10.9,7.3Hz,1H),3.12 - 3.04(m,1H),2.80(q,J=7.5Hz,2H),2.34 - 2.18(m,5H),1.24(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.13,154.46,143.72,143.69,137.71,137.42,133.91,130.48,130.27,128.47,127.75,126.64,125.28,124.49,123.95,122.92,75.43,56.49,54.41,53.56,43.70,27.76,25.25,14.55,11.46.MS(ESI)(m/z):[M+H]$^+$463.20

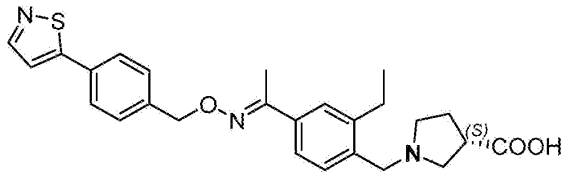
[0374] (S,E)-1-(2-乙基-4-(1-((4-(异噻唑-4-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸的(化合物74)结构



[0375] 淡黄色固体，产率11.6%。^{1}H NMR(500MHz,CD_3OD) δ 9.07(s,1H),8.86(s,1H),7.72 - 7.68(m,2H),7.63(d,J=1.9Hz,1H),7.57(dd,J=8.1,1.9Hz,1H),7.52(d,J=8.1Hz,1H),7.50 - 7.46(m,2H),5.26(s,2H),4.46 - 4.37(m,2H),3.52(dd,J=11.3,6.0Hz,1H),3.44 - 3.39(m,1H),3.39(d,J=4.0Hz,1H),3.35(d,J=6.9Hz,1H),3.12(ddd,J=14.4,8.7,5.9Hz,1H),2.82(q,J=7.5Hz,2H),2.37 - 2.22(m,5H),1.24(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.11,155.89,154.49,143.75,143.06,139.51,138.10,137.76,131.87,130.56,130.04,

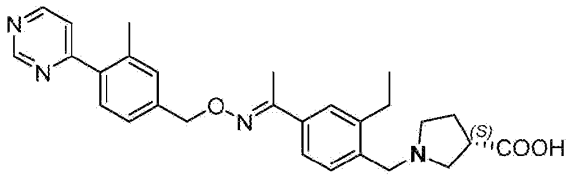
128.57,126.66,126.46,123.98,75.38,56.36,54.37,53.59,43.65,27.77,25.29,14.57,11.44.MS(ESI)(m/z):[M+H]$^+$464.20

[0376] (S,E)-1-(2-乙基-4-(1-((4-(异噻唑-5-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物75)的结构



[0377] 淡黄色固体，产率14.9%。^{1}H NMR(500MHz,CD_3OD) δ 8.48(d,J=1.8Hz,1H),7.72 - 7.66(m,2H),7.63(d,J=1.9Hz,1H),7.60(d,J=1.8Hz,1H),7.57(dd,J=8.0,1.9Hz,1H),7.52(s,2H),7.51(s,1H),5.27(s,2H),4.46 - 4.36(m,2H),3.52(dd,J=11.3,5.9Hz,1H),3.43 - 3.38(m,1H),3.36(dd,J=12.2,5.6Hz,2H),3.12(dq,J=11.3,4.4,2.9Hz,1H),2.82(q,J=7.5Hz,2H),2.38 - 2.23(m,5H),1.24(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 177.97,167.11,158.52,154.68,143.76,140.25,137.69,130.55,130.11,129.81,128.63,126.67,126.35,123.99,119.97,75.14,56.38,54.37,53.58,43.64,27.77,25.28,14.56,11.44.MS(ESI)(m/z):[M+H]$^+$464.20

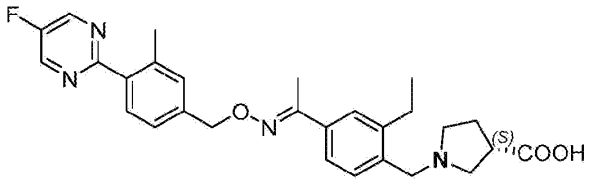
[0378] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(嘧啶-4-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物76)的结构



[0379] 淡黄色固体，产率19.9%。^{1}H NMR(500MHz,CD_3OD) δ 9.21(d,J=1.4Hz,1H),8.83(d,J=5.3Hz,1H),7.65(dt,J=3.4,1.5Hz,2H),7.59(dd,J=8.1,1.9Hz,1H),7.49(dd,J=7.8,6.3Hz,2H),7.39(d,J=8.6Hz,2H),5.28(s,2H),4.49 - 4.39(m,2H),3.56(dd,J=11.3,5.6Hz,1H),3.45 - 3.34(m,2H),3.30(t,J=5.6Hz,1H),3.13(p,J=7.2Hz,1H),2.83(q,J=7.5Hz,2H),2.43(s,3H),2.41 - 2.32(m,1H),2.30(s,3H),2.29 - 2.23(m,1H),1.26(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 167.30,157.63,156.90,154.54,143.78,140.16,137.83,136.66,1

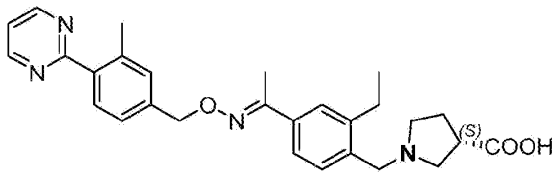
36.11,130.53,130.43,129.94,129.44,126.71,125.53,124.02,121.62,75.26,56.40,54.34,53.54,29.38,27.65,25.24,19.11,14.57,11.41.MS(ESI)(m/z):$[M+H]^+$473.20

[0380] (S,E)-1-(2-乙基-4-(1-(((4-(5-氟嘧啶-2-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物77)的结构



[0381] 淡黄色固体，产率15.4%。^{1}H NMR(500MHz,CD_3OD) δ 8.82(d,J=1.9Hz,2H),7.76(d,J=7.7Hz,1H),7.64(d,J=2.0Hz,1H),7.57(dd,J=8.1,2.0Hz,1H),7.48(d,J=8.1Hz,1H),7.35(d,J=8.9Hz,2H),5.26(s,2H),4.44 - 4.34(m,2H),3.52(dd,J=11.3,5.4Hz,1H),3.41 - 3.33(m,2H),3.32 - 3.25(m,1H),3.10(s,1H),2.82(q,J=7.6Hz,2H),2.51(s,3H),2.29(d,J=1.4Hz,5H),1.25(td,J=7.5,1.7Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 163.34,157.57,155.48,154.51,144.66,144.50,143.73,139.67,137.77,137.07,136.48,130.50,130.46,130.20,130.14,126.67,125.12,123.98,75.35,56.58,54.40,53.55,29.35,27.76,25.23,19.92,14.55,11.43.MS(ESI)(m/z):$[M+H]^+$491.20

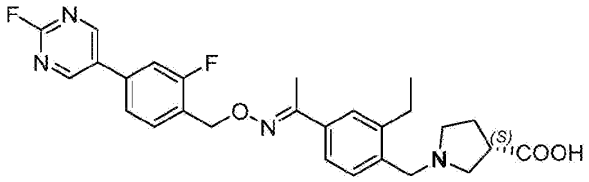
[0382] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(嘧啶-2-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物78)的结构



[0383] 淡黄色固体，产率21.4%。^{1}H NMR(500MHz,CD_3OD) δ 8.89(d,J=4.9Hz,2H),7.69(d,J=7.9Hz,1H),7.65(d,J=1.9Hz,1H),7.59(dd,J=8.0,1.9Hz,1H),7.52(d,J=8.1Hz,1H),7.44(t,J=5.0Hz,1H),7.37(d,J=7.2Hz,2H),5.27(s,2H),4.47 - 4.39(m,2H),3.56(dd,J=11.3,5.9Hz,1H),3.42(dt,J=11.2,7.4Hz,2H),3.35(d,J=7.0Hz,1H),3.15(td,J=8.6,4.1Hz,1H),2.83(q,J=7.5Hz,2H),2.48(s,3H),2.35(dd,J=14.4,7.4Hz,1H),2.30(s,4H),1.26(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 167.16,157.00,154.46,143.78,139.72,137.8

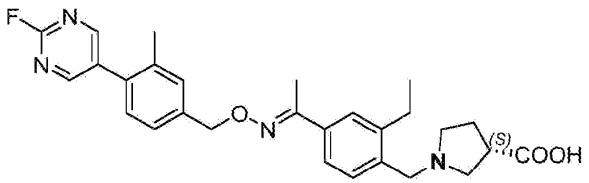
6,137.42,136.88,130.58,130.37,129.95,129.87,126.70,125.17,124.01,119.06,75.37,56.32,54.38,53.60,43.49,27.71,25.29,19.54,14.57,11.41.MS(ESI)(m/z):$[M+H]^+$473.20

[0384] (S,E)-1-(2-乙基-4-(1-(((2-氟-4-(2-氟嘧啶-5-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物79)的结构



[0385] 淡黄色固体，产率14.3%。^{1}H NMR(500MHz,CD_3OD) δ 8.98(d,J=1.4Hz,2H),7.67 - 7.62(m,2H),7.57(dd,J=8.0,1.9Hz,1H),7.52(t,J=8.6Hz,3H),5.34(s,2H),4.47 - 4.37(m,2H),3.54(dd,J=11.4,5.8Hz,1H),3.43 - 3.36(m,2H),3.35(s,1H),3.18 - 3.09(m,1H),2.83(q,J=7.5Hz,2H),2.39 - 2.29(m,1H),2.27(s,4H),1.25(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 163.34,162.29,161.60,160.32,159.08,158.99,154.85,143.77,137.60,131.55,131.52,130.54,130.13,126.66,126.05,125.93,123.98,122.45,113.63,113.45,68.93,56.36,54.37,53.60,43.53,27.71,25.25,14.52,11.28.MS(ESI)(m/z):$[M+H]^+$495.20

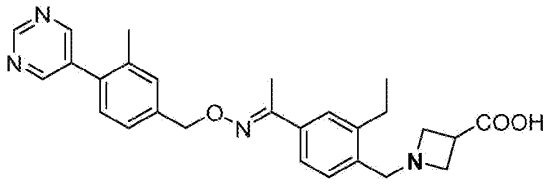
[0386] (S,E)-1-(2-乙基-4-(1-(((4-(2-氟嘧啶-5-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物80)的结构



[0387] 淡黄色固体，产率22.2%。^{1}H NMR(500MHz,CD_3OD) δ 8.69(d,J=1.6Hz,2H),7.64(d,J=1.9Hz,1H),7.57(dd,J=8.1,1.9Hz,1H),7.49(d,J=8.1Hz,1H),7.41(s,1H),7.38(dd,J=7.8,1.8Hz,1H),7.27(d,J=7.8Hz,1H),5.25(s,2H),4.42 - 4.34(m,2H),3.51(dd,J=11.1,5.7Hz,1H),3.35(t,J=3.5Hz,2H),3.31 - 3.24(m,1H),3.10(td,J=8.7,8.0,4.3Hz,1H),2.82(q,J=7.5Hz,2H),2.30(s,4H),2.28(s,4H),1.25(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 177.99,162.77,161.05,160.69,160.59,157.18,154.51,143.71,139.35,137.62,135.80,

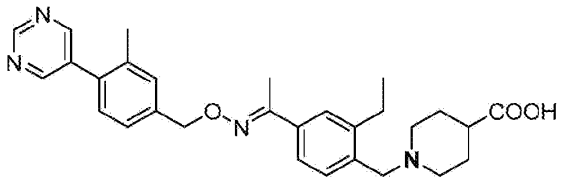
133.62,133.58,132.50,130.47,130.44,130.16,129.72,126.62,125.87,123.94,75.29,56.58,54.39,53.55,43.69,27.75,25.24,18.95,14.56,11.40.MS(ESI)(m/z):[M+H]$^+$491.20

[0388] (E)-1-(2-乙基-4-(1-(((3-甲基-4-(嘧啶-5-基)苄基)氧基)亚氨基)乙基)苄基)氮杂环丁烷-3-羧酸(化合物81)的结构



[0389] 淡黄色固体，产率35.6%。^{1}H NMR(500MHz,CD_3OD) δ 9.15(s,1H),8.85 - 8.75(m,2H),7.63(s,1H),7.56(d,J=8.1Hz,1H),7.45 - 7.35(m,3H),7.26(t,J=6.5Hz,1H),5.25(d,J=3.0Hz,2H),4.40(s,2H),4.16(p,J=9.5Hz,4H),3.41(p,J=8.3Hz,1H),2.80(q,J=7.5Hz,2H),2.30(s,3H),2.27(s,3H),1.27 - 1.22(m,3H).^{13}C NMR(126MHz,CD_3OD) δ 176.27,156.56,156.36,154.50,143.54,139.32,137.57,135.63,133.39,130.18,129.64,129.54,126.62,125.90,123.97,75.30,57.16,54.94,34.92,25.19,18.97,14.46,11.41.MS(ESI)(m/z):[M+H]$^+$459.20

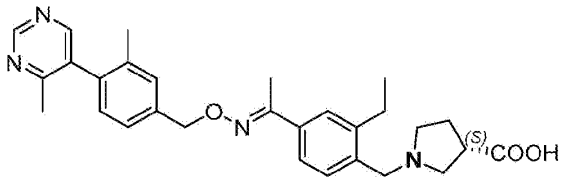
[0390] (E)-1-(2-乙基-4-(1-(((3-甲基-4-(嘧啶-5-基)苄基)氧基)亚氨基)乙基)苄基)哌啶-4-羧酸(化合物82)的结构



[0391] 淡黄色固体，产率30.3%。^{1}H NMR(500MHz,CD_3OD) δ 9.15(s,1H),8.80(s,2H),7.63(d,J=1.9Hz,1H),7.56(dd,J=8.1,1.9Hz,1H),7.47(d,J=8.1Hz,1H),7.42(s,1H),7.39(dd,J=7.8,1.7Hz,1H),7.27(d,J=7.8Hz,1H),5.26(s,2H),4.13(s,2H),3.30 - 3.27(m,1H),2.90 - 2.78(m,4H),2.46 - 2.32(m,2H),2.31(s,3H),2.29(s,3H),2.05(dd,J=14.6,4.0Hz,2H),1.90(q,J=12.8,12.2Hz,2H),1.25(t,J=7.5Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 179.59(d,J=2.2Hz),156.57,156.35,154.63,144.37,139.34,137.46,135.63,135.60,133.38,131.20,13

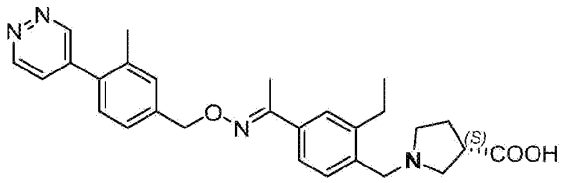
0.18,129.63,126.58,125.90,123.73,75.28,57.31,52.14,40.79,26.66,25.39,18.97,14.65,11.45.MS(ESI)(m/z):$[M+H]^+$487.30

[0392] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(4-甲基嘧啶-5-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物83)的结构



[0393] 淡黄色固体，产率42.5%。^{1}H NMR(500MHz,Methanol-d_4) δ 9.03(s,1H),8.48(s,1H),7.66(d,J=1.9Hz,1H),7.59(dd,J=8.1,1.9Hz,1H),7.51(d,J=8.1Hz,1H),7.43(d,J=1.7Hz,1H),7.38(dd,J=7.8,1.7Hz,1H),7.17(d,J=7.8Hz,1H),5.28(s,2H),4.48 - 4.36(m,2H),3.53(d,J=7.7Hz,1H),3.43 - 3.37(m,2H),3.31(s,1H),3.13(s,1H),2.84(q,J=7.5Hz,2H),2.33(s,4H),2.30(s,4H),2.11(s,3H),1.27(t,J=7.5Hz,3H).^{13}C NMR(126MHz,Methanol-d_4) δ 165.58,156.48,156.26,154.49,143.76,139.12,137.77,135.87,134.85,134.16,130.53,130.18,129.81,129.17,126.68,125.69,124.00,75.40,56.58,54.41,53.58,48.46,27.77,25.25,20.95,18.56,14.57,11.43.MS(ESI)(m/z):$[M+H]^+$487.30

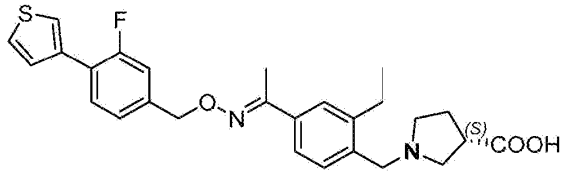
[0394] (S,E)-1-(2-乙基-4-(1-(((3-甲基-4-(哒嗪-4-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物84)的结构



[0395] 淡黄色固体，产率27.3%。^{1}H NMR(500MHz,CD_3OD) δ 9.27 - 9.23(m,2H),7.77(dd,J=5.3,2.4Hz,1H),7.65(d,J=1.9Hz,1H),7.58(dd,J=8.1,1.9Hz,1H),7.48(d,J=8.0Hz,1H),7.45(s,1H),7.42(dd,J=7.8,1.7Hz,1H),7.34(d,J=7.8Hz,1H),5.28(s,2H),4.36(d,J=2.5Hz,2H),3.47(dd,J=11.1,6.0Hz,1H),3.37 - 3.34(m,1H),3.31(d,J=7.1Hz,1H),3.27(q,J=9.5,8.4Hz,1H),3.09(ddd,J=12.3,8.4,5.8Hz,1H),2.83(q,J=7.5Hz,2H),2.36(s,3H),2.33 - 2.22(m,5H),1.27(t,J=7.5Hz,3H).^{13}C NMR(151MHz,CD_3OD) δ 178.13,154.62,151.

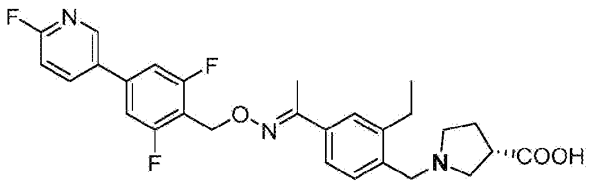
80,150.95,143.69,141.24,139.97,137.58,135.47,134.18,130.41,130.34,129.36,127.39,126.63,125.97,123.94,75.20,56.73,54.58,53.60,43.75,27.78,25.22,18.89,14.54,11.39.MS(ESI)(m/z):$[M+H]^+$473.30

[0396] (S,E)-1-(2-乙基-4-(1-(((3-氟-4-(噻吩-3-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物85)的结构



[0397] 淡黄色固体，产率26.5%。^{1}H NMR(500MHz,CD_3OD) δ 7.66(dt,J=2.8,1.4Hz,1H),7.64 - 7.59(m,2H),7.55(dd,J=8.1,1.9Hz,1H),7.49 - 7.45(m,2H),7.44(dt,J=5.1,1.4Hz,1H),7.26 - 7.18(m,2H),5.23(s,2H),4.39 - 4.30(m,2H),3.49(dd,J=11.1,5.8Hz,1H),3.35(d,J=9.5Hz,1H),3.32 - 3.30(m,1H),3.25(ddd,J=14.6,7.7,3.8Hz,1H),3.08(ddd,J=14.6,8.7,5.8Hz,1H),2.79(q,J=7.6Hz,2H),2.33 - 2.20(m,5H),1.23(t,J=7.6Hz,3H).^{13}C NMR(126MHz,CD_3OD) δ 178.15,160.47,158.51,154.74,143.70,139.64,139.58,137.55,135.32,135.31,130.48,130.44,129.15,129.11,127.08,127.05,126.63,125.21,123.94,123.69,123.67,123.14,123.08,122.77,122.67,115.25,115.06,74.68,56.49,54.38,53.55,43.69,27.75,25.23,14.53,11.45.MS(ESI)(m/z):$[M+H]^+$481.20

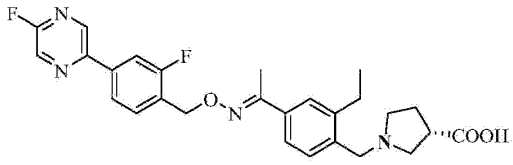
[0398] (S,E)-1-(2-乙基-4-(1-(((2,6-二氟-4-(6-氟吡啶-3-基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物86)的结构



[0399] 淡黄色固体，产率26.9%。^{1}H NMR(500MHz,CD_3OD) δ 8.49(d,J=2.6Hz,1H),8.22(ddd,J=8.5,7.5,2.7Hz,1H),7.64(d,J=1.9Hz,1H),7.56(dd,J=8.1,1.9Hz,1H),7.47(d,J=8.1Hz,1H),7.35(d,J=8.3Hz,2H),7.19 - 7.15(m,1H),5.33(s,2H),4.42 - 4.34(m,2H),3.51(dd,J=11.2,5.8Hz,1H),3.39 - 3.34(m,2H),3.32 - 3.25(m,1H),3.10(ddd,J=14.4,8.5,5.8

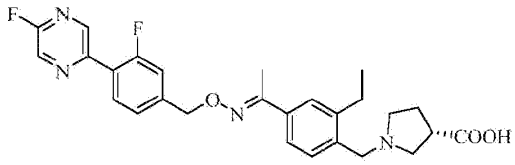
Hz,1H),2.81(q,J＝7.6Hz,2H),2.36－2.24(m,2H),2.20(s,3H),1.26(t,J＝7.3Hz,3H).^{13}CNMR(126MHz,CD_3OD) δ 172.97,165.98,164.82,164.08,162.83,156.01,146.90,146.78,145.01,141.80,141.73,140.95,138.87,131.81,127.93,125.25,114.64,111.05,111.03,110.84,110.74,64.06,57.88,55.90,55.04,45.00,29.11,26.57,20.85,15.78,12.33.MS(ESI)(m/z):[M+H]$^+$512.20

[0400] (S,E)－1－(2－乙基－4－(1－(((2－氟－4－(5－氟吡嗪－2－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物87)的结构



[0401] 白色固体，产率78.9％。^{1}H NMR(500MHz,Methanol－d_4) δ 8.77(s,1H),8.56(s,1H),7.90－7.79(m,2H),7.65－7.59(m,2H),7.56(s,1H),7.48(d,J＝8.1Hz,1H),5.34(s,2H),4.44－4.34(m,2H),3.55－3.46(m,1H),3.36(d,J＝7.7Hz,1H),3.28(dd,J＝10.9,7.3Hz,1H),3.13－3.05(m,1H),2.81(q,J＝8.6Hz,2H),2.33(dt,J＝15.2,7.9Hz,1H),2.28(s,3H),2.23(dd,J＝13.5,6.8Hz,1H),2.03(s,1H),1.28－1.21(m,3H).^{13}C NMR(126MHz,Methanol－d_4) δ 154.84,143.72,138.45,138.38,137.57,132.58,132.27,131.05,130.46,130.30,126.64,123.95,121.93,113.21,113.02,69.00,56.53,54.37,53.56,43.58,27.71,25.21,11.29.MS(m/z):[M+H]$^+$495.20

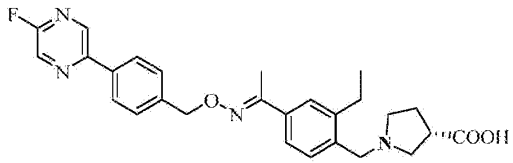
[0402] (S,E)－1－(2－乙基－4－(1－(((3－氟－4－(5－氟吡嗪－2－基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷－3－羧酸(化合物88)的结构



[0403] 黄色固体，产率75.0％。^{1}H NMR(500MHz,Methanol－d_4) δ 8.67(s,1H),8.62(d,J＝8.3Hz,1H),7.63(s,1H),7.56(d,J＝7.4Hz,1H),7.49(d,J＝8.1Hz,1H),7.38(d,J＝8.0Hz,1H),7.32(d,J＝12.1Hz,1H),5.30(s,2H),4.37(d,J＝11.1Hz,2H),3.29(t,J＝6.7Hz,1H),3.09(t,J＝7.6Hz,1H),2.82(q,J＝7.5Hz,2H),2.31(s,3H),2.26－2.17(m,1H),2.03(s,1H),1.95(s,1H),1.

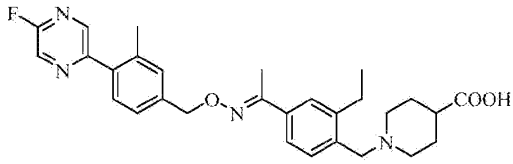
24(t,J＝7.5Hz,3H).^{13}C NMR(126MHz,Methanol−d_4) δ 155.04,143.70,143.17,141.41,141.34,141.24,137.37,132.95,132.65,130.83,130.54,130.52,130.46,126.61,123.93,123.82,115.16,114.98,74.39,56.65,54.53,53.57,43.85,25.24,14.52,11.44.MS(m/z):[M+H]$^+$495.20

[0404] (S,E)−1−(2−乙基−4−(1−((4−(5−氟吡嗪−2−基)苄基)氧基)亚氨基)乙基)苄基)吡咯烷−3−羧酸(化合物89)的结构



[0405] 白色固体，产率76.6％。^{1}H NMR(500MHz,Methanol−d_4) δ 8.79 - 8.69(m,1H),8.58 - 8.51(m,1H),8.03(dd,J＝16.8,5.3Hz,2H),7.63(d,J＝7.0Hz,1H),7.58 - 7.54(m,3H),7.47(d,J＝8.1Hz,1H),5.30(s,2H),4.41 - 4.30(m,2H),3.50(dd,J＝10.7,5.5Hz,1H),3.37(s,1H),3.28 - 3.20(m,1H),3.09(dd,J＝10.2,4.2Hz,1H),2.85 - 2.78(m,2H),2.36 - 2.31(m,1H),2.30(s,3H),2.24(q,J＝6.9,6.4Hz,1H),1.28 - 1.20(m,3H).^{13}C NMR(126MHz,Methanol−d_4) δ 154.62,143.69,140.08,138.24,138.17,132.34,132.04,130.43,128.28,126.65,126.44,123.94,75.24,56.57,54.45,53.58,43.66,27.73,25.22,14.53,11.42.MS(m/z):[M+H]$^+$477.20

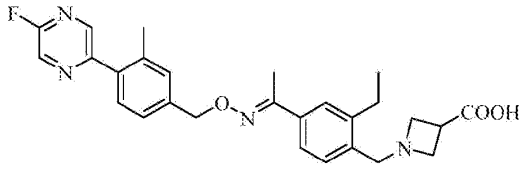
[0406] (E)−1−(2−乙基−4−(1−(((3−甲基−4−(5−氟吡嗪−2−基)−苄基)氧基)亚氨基)乙基)苄基)哌啶−4−羧酸(化合物90)的结构



[0407] 白色固体，产率28.8％。^{1}H NMR(500MHz,Methanol−d_4) δ 8.58(d,J＝8.2Hz,1H),8.37(s,1H),7.60(s,1H),7.52(d,J＝10.0Hz,1H),7.41(dd,J＝18.7,7.9Hz,4H),5.26(s,2H),3.96(s,2H),3.18(d,J＝11.6Hz,2H),2.80(q,J＝7.6Hz,2H),2.66(d,J＝11.5Hz,2H),2.38(s,3H),2.33(d,J＝15.1Hz,1H),2.28(s,3H),2.02 - 1.93(m,2H),1.84(d,J＝12.0Hz,2H),1.24(t,J＝7.6Hz,3H).^{13}C NMR(126MHz,Methanol−d_4) δ 158.27,154.80,144.11,141.30,139.50,13

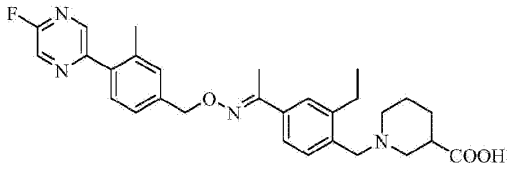
6.91,136.35,131.93,131.63,130.86,130.33,129.57,126.42,125.50,123.52,75.26,57.89,52.46,27.35,25.33,19.05,14.60,11.48.MS(m/z):[M+H]$^+$505.20

[0408] (E)-1-(2-乙基-4-(1-(((3-甲基4-(5-氟吡嗪-2-基)-苄基)氧基)亚氨基)乙基)苄基)氮杂环丁烷-3-羧酸(化合物91)的结构



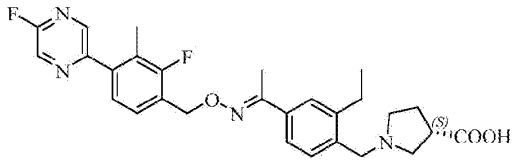
[0409] 白色固体，产率62.5%。^{1}H NMR(500MHz,Methanol-d_4) δ 8.58(d,J=8.3Hz,1H),8.37(s,1H),7.63(s,1H),7.56(d,J=8.0Hz,1H),7.40(dd,J=19.3,7.9Hz,4H),5.26(s,2H),4.40(s,2H),4.16(d,J=8.3Hz,4H),2.79(q,J=7.5Hz,3H),2.37(s,7H),2.28(s,3H),1.25(t,J=7.5Hz,3H).^{13}C NMR(126MHz,Methanol-d_4) δ 176.26,160.27,158.28,154.47,152.86,143.53,141.29,141.22,139.45,137.66,136.37,131.94,131.64,130.32,129.57,129.51,126.66,125.50,123.98,75.33,57.18,54.93,34.86,25.16,19.04,14.45,11.39.MS(m/z):[M+H]$^+$477.20

[0410] (E)-1-(2-乙基-4-(1-(((3-甲基4-(5-氟吡嗪-2-基)-苄基)氧基)亚氨基)乙基)苄基)哌啶-3-羧酸(化合物92)的结构



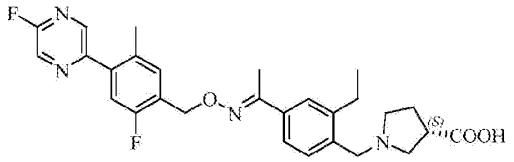
[0411] 白色固体，产率83.5%。^{1}H NMR(500MHz,Methanol-d_4) δ 8.58(d,J=7.0Hz,1H),8.37(s,1H),7.65(s,1H),7.57(d,J=8.0Hz,1H),7.48(d,J=8.1Hz,2H),7.45 - 7.35(m,6H),5.26(s,5H),4.23(d,J=3.6Hz,5H),3.37(s,4H),3.12(d,J=10.1Hz,5H),2.82(dq,J=14.9,7.3Hz,3H),2.65(s,2H),2.38(s,7H),2.29(s,6H),1.85(d,J=48.6Hz,11H),1.27(t,J=7.5Hz,6H).^{13}C NMR(126MHz,Methanol-d_4) δ 160.27,158.28,154.54,152.92,144.11,141.30,141.22,139.48,137.76,136.37,135.06,131.94,131.64,130.98,130.33,129.58,126.60,125.51,123.93,75.33,54.53,52.79,48.46,25.20,19.04,14.45,11.41.MS(m/z):[M+H]$^+$505.20

[0412] (S，E)-1-(2-乙基-4-(1-(((2-氟-4-(5-氟吡嗪-2-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物93)的结构



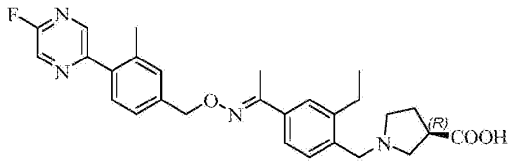
[0413] 白色固体，产率70.1％。^{1}H NMR(500MHz,Methanol-d_4) δ 8.59(d,J＝8.2Hz,1H),8.37(s,1H),7.63(s,1H),7.56(d,J＝8.0Hz,1H),7.49(d,J＝8.1Hz,1H),7.42(t,J＝7.5Hz,1H),7.25(d,J＝7.9Hz,1H),5.33(s,2H),4.44－4.33(m,2H),3.52(dd,J＝11.2,5.6Hz,1H),3.41－3.35(m,2H),3.28(dt,J＝10.8,7.3Hz,1H),3.10(dq,J＝8.7,4.3,2.9Hz,1H),2.81(q,J＝7.5Hz,2H),2.27(s,8H),1.24(t,J＝7.4Hz,3H).^{13}C NMR(126MHz,Methanol-d_4) δ 177.94,160.40,160.38,158.43,158.40,154.73,151.66,143.71,141.43,141.35,137.54,132.19,131.88,130.49,130.34,127.45,127.41,126.63,125.98,125.85,124.93,124.90,123.94,123.68,123.54,69.41,69.38,56.46,54.32,53.54,43.62,27.73,25.23,14.53,11.32,10.54,10.49.MS(m/z):[M+H]$^{+}$509.19

[0414] (S，E)-1-(2-乙基-4-(1-(((2-氟-4-(5-氟吡嗪-2-基)-5-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物94)的结构



[0415] 白色固体，产率71.5％。^{1}H NMR(500MHz,Methanol-d_4) δ 8.60(dd,J＝8.2,1.4Hz,1H),8.41(t,J＝1.5Hz,1H),7.65(d,J＝1.9Hz,1H),7.58(dd,J＝8.1,1.9Hz,1H),7.48(d,J＝8.1Hz,1H),7.45(d,J＝7.2Hz,1H),7.25(d,J＝10.3Hz,1H),5.31(s,2H),4.43－4.35(m,2H),3.52(dd,J＝11.2,5.8Hz,1H),3.39－3.35(m,2H),3.29(dd,J＝12.9,5.5Hz,1H),3.11(ddd,J＝14.4,8.7,5.8Hz,1H),2.82(q,J＝7.5Hz,2H),2.35(s,3H),2.33－2.30(m,1H),2.27(s,3H),2.24(dd,J＝13.7,6.5Hz,1H),1.25(d,J＝7.5Hz,3H).^{13}C NMR(126MHz,Methanol-d_4) δ 178.22,160.41,160.09,158.41,158.14,154.72,151.50,143.70,141.35,141.27,137.60,136.95,133.09,133.05,132.26,132.08,131.96,130.46,130.37,126.65,125.86,125.74,123.96,116.17,115.99,69.06,56.50,54.48,53.62,43.57,27.71,25.21,18.32,14.50,11.27.MS(m/z):[M+H]$^{+}$509.20

[0416] (R,E)-1-(2-乙基-4-(1-(((4-(5-氟吡嗪-2-基)-3-甲基苄基)氧基)亚氨基)乙基)苄基)吡咯烷-3-羧酸(化合物95)的结构



[0417] 淡黄色固体，产率21.4%。^{1}H NMR(500MHz,Methanol-d_4) δ 8.57(dd,J=8.3,1.3 Hz,1H),8.36(t,J=1.5Hz,1H),7.64(d,J=1.9Hz,1H),7.57(dd,J=8.1,1.9Hz,1H),7.49(d,J=8.1Hz,1H),7.41(d,J=7.8Hz,1H),7.39 - 7.34(m,2H),5.26(s,2H),4.44 - 4.34(m,2H),3.52(dd,J=11.2,5.7Hz,1H),3.37(td,J=9.1,8.2,3.3Hz,2H),3.28(dt,J=11.0,7.4Hz,1H),3.10(ddd,J=14.5,8.8,5.7Hz,1H),2.82(q,J=7.5Hz,2H),2.37(s,3H),2.32(td,J=7.9,3.6Hz,1H),2.28(s,3H),2.27 - 2.22(m,1H),1.25(t,J=7.5Hz,3H).^{13}C NMR(126MHz,Methanol-d_4) δ 177.86,160.26,158.26,154.49,152.89,152.85,143.73,141.28,141.21,139.46,137.71,136.37,135.07,135.06,131.94,131.64,130.50,130.33,130.21,129.58,126.65,125.50,123.96,75.34,56.48,54.34,53.54,43.60,27.72,25.24,19.06,14.55,11.42.MS(ESI)(m/z):$[M+H]^+$491.25.

[0418] 实施例2.S1PR4激动剂生物活性测试

[0419] 一、实验原理

[0420] Tango检测技术通过β-arrestin和GPCR的相互作用来检测配体依赖的GPCR活性。TEV分离技术是利用TEV蛋白酶的两个非活性片段(NTEV，1-118和CTEV，119-221)的互补来重建功能蛋白酶，将NTEV片段和人工转录因子四环素反式激活因子(tTA)融合到GPCR的C端，CTEV片段融合到人的β-arrestin 2。为了提高GPCR与β-arrestin相互作用的稳定性，在GPCR和NTEV之间引入了人精氨酸加压素受体2的C末端的一个短序列(V2 tail)。V2 tail含有多个GRK磷酸化位点，这些位点在磷酸化后能增强β-arrestin的结合。CTEV片段携带稳定点突变S219P，在221氨基酸处被截短，以去除自抑制的C端尾，同时将β-arrestin 2截短，使缺失整个C端尾(缺少氨基酸383-410)，截短具有较强的刺激依赖性受体脱敏作用，因此与野生型β-arrestin 2相比，提高了检测的敏感性。UAS报告结构由上游激活序列元件(Upstream activesequence，UAS)、CMV最小启动子和tTA依

赖性荧光素酶报告基因组成。因此构建Tango细胞需将上述三个质粒同时转染至细胞。GPCR在被激活招募β-arrestin后，β-arrestin末端的TEV酶将tTA从GPCR末端切除，游离的tTA将启动tTA依赖的荧光素酶转录，最终通过检测荧光强度来判断化合物的活性。

[0421] 二、实验过程

[0422] 1)将Tango细胞株分别从培养皿上消化下来，通过细胞计数，以每孔10000个细胞的密度，700μL/well铺板至白色不透明96孔板上(四周加60μL D'hanks)，37℃的5%的CO2培养箱中培养过夜(20h)，第二天细胞密度90%左右；

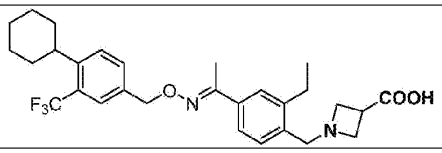
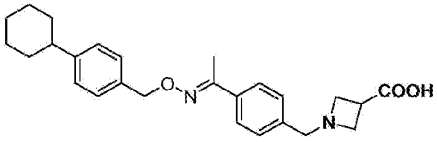
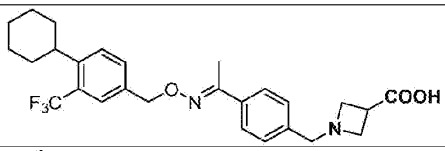
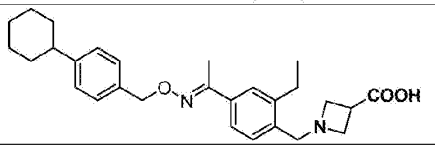
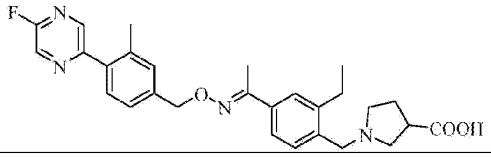
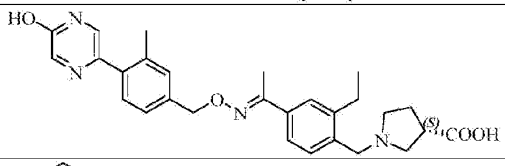
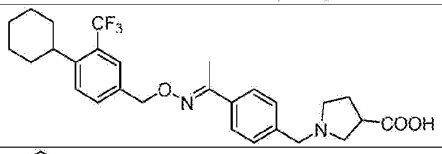
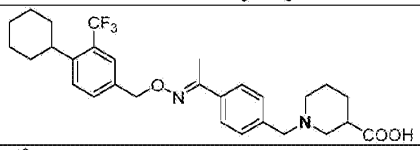
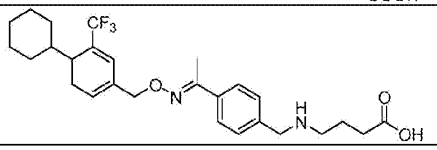
[0423] 2)20h后，每孔加入30μL梯度稀释的化合物溶液，对照组添加30μL F12K完全培养基，每组三个复孔；

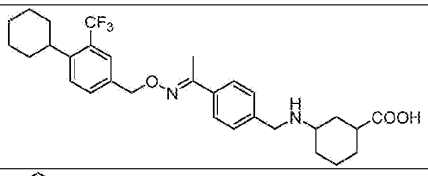
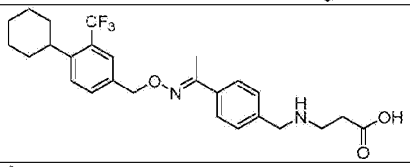
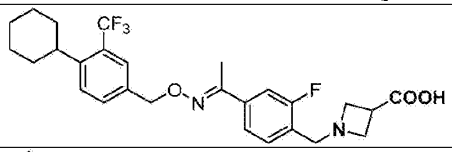
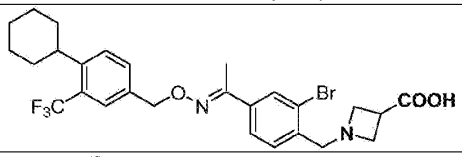
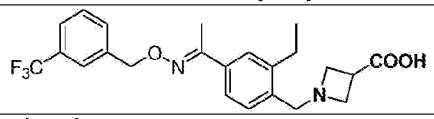
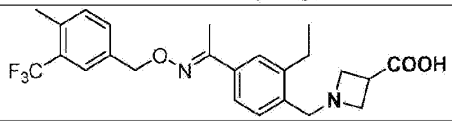
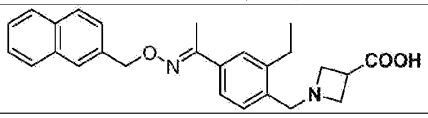
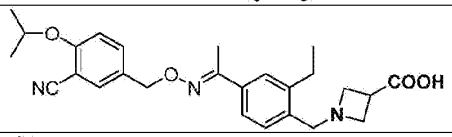
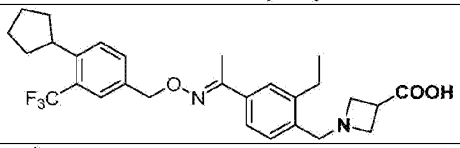
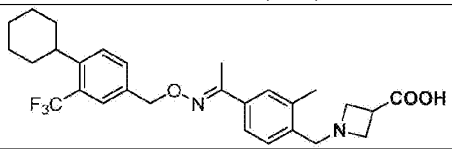
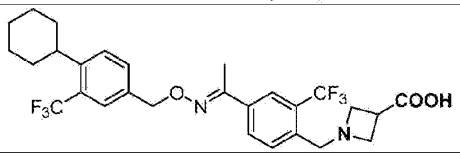
[0424] 3)药物作用20h收样，培养箱中取出细胞，用Bright Glo™Luciferase Assay进行荧光素酶分析：每孔加入5μL试剂，室温下避光轻轻摇晃10min后检测；

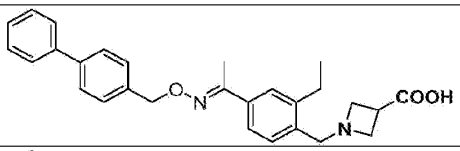
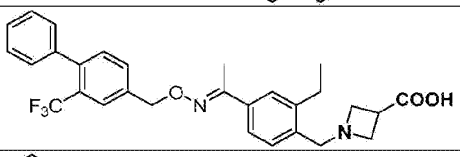
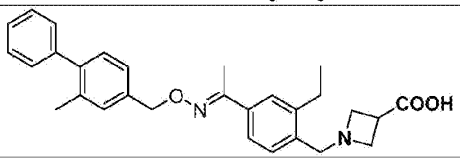
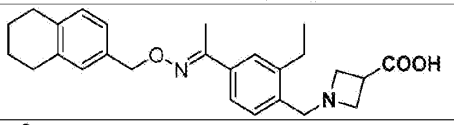
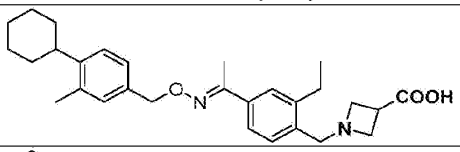
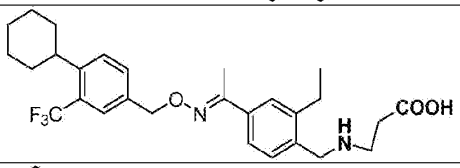
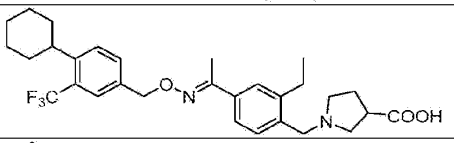
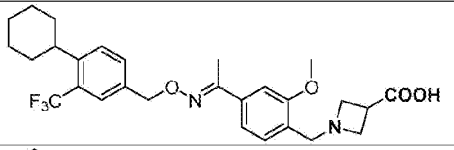
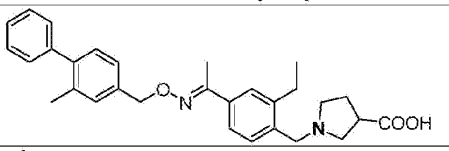
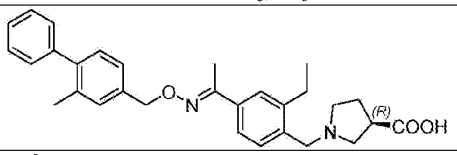
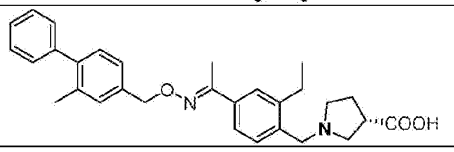
[0425] 4)置于酶标仪读数，测定Relative light unit(RLU)，记录荧光(Luminescence)数值，通过Graphpad prism软件进行数据处理，计算出化合物的EC50。

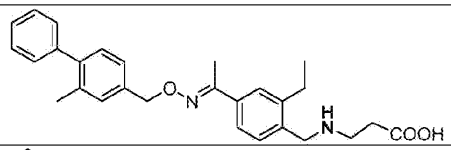
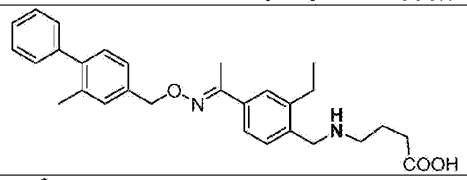
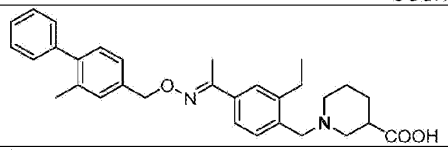
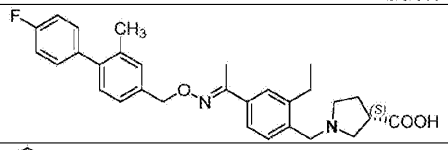
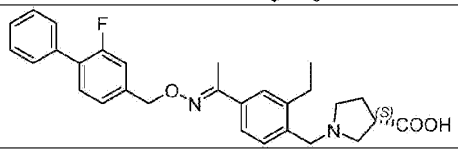
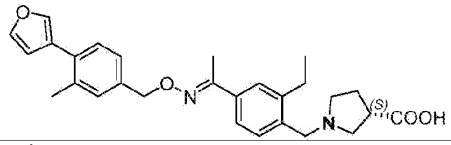
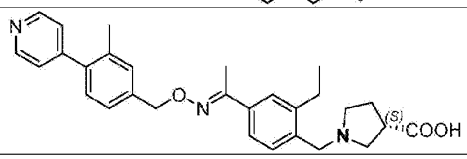
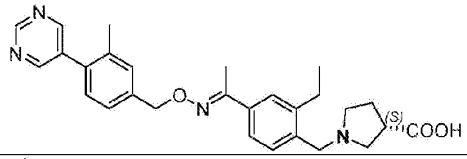
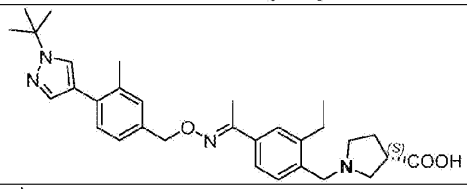
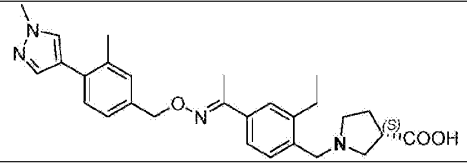
[0426] 三、测试结果：

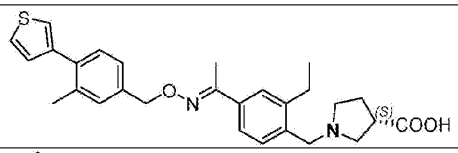
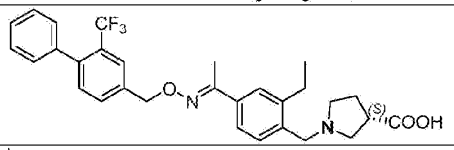
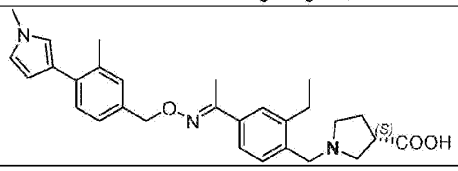
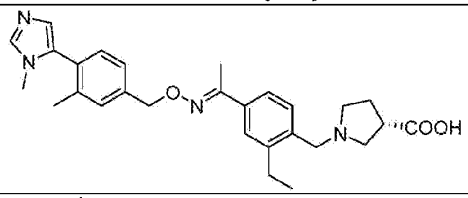
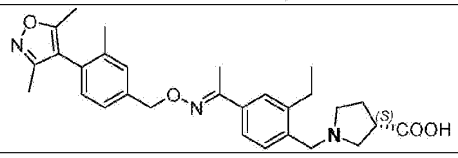
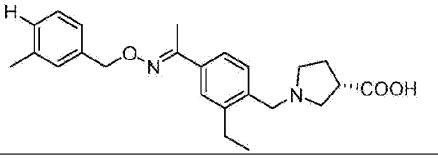
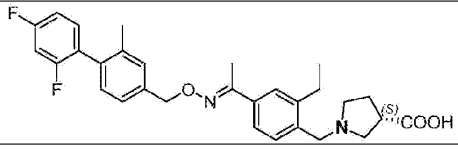
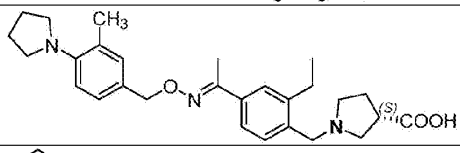
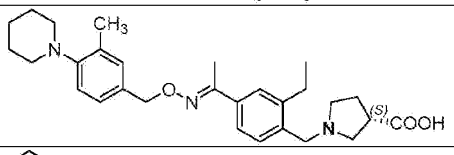
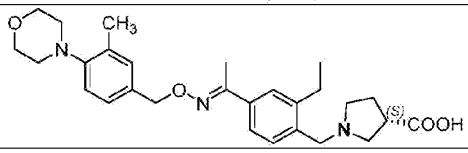
[0427] (化合物均为45μM终浓度测试，9个梯度，5倍稀释。S1PR1以1μM BAF-312为阳性对照，S1PR4以25μM BAF-312为阳性对照)

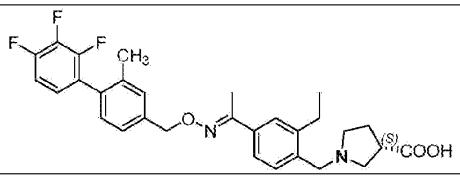
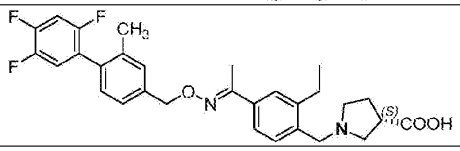
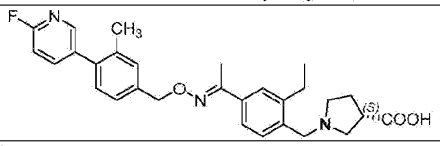
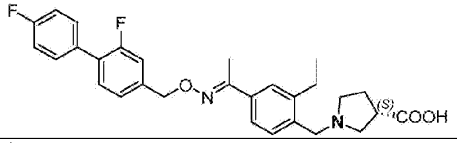
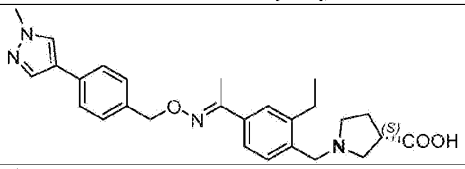
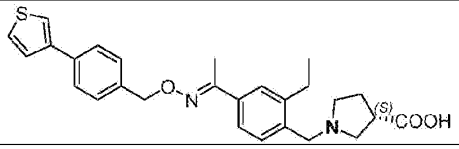
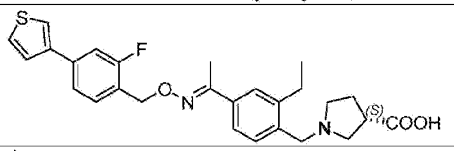
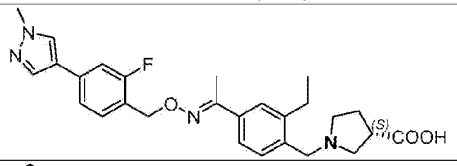
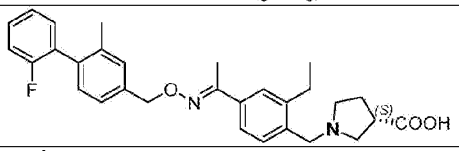
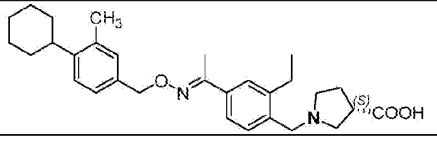
化合物编号	结构式	Tango-hS1P1-CHO EC_{50}(nM)	Tango-hS1P4-CHO EC_{50}(nM)	Tango-hS1P4-R-79C-CHO EC_{50}(nM)
BAF312		1.04±0.10	155.44±21.75	157.15±7.90
1		698.90±157.79	2969.00±471.63	1908.00±798.15
2		4.48±0.26	324.45±24.55	236.94±54.45
3		578.00±102.33	2157.00±771.50	1338.00±278.75
4		**162.2±23.44**	**10.59±1.19**	
5		**133.2±23.44**	**4.22±1.19**	
6		21.77±3.02	318.40±81.40	291.50±95.50
7		508.40±86.94	2504.00±518.88	3822.00±1320.00
8		51.64±0.38	2399.00±157.50	728.70±64.50

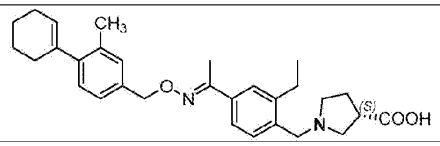
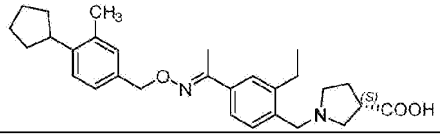
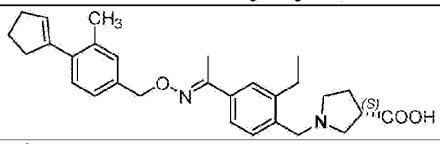
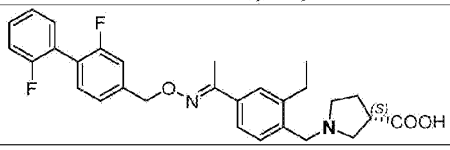
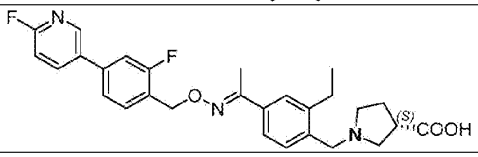
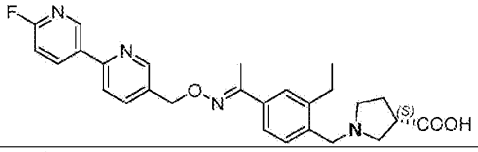
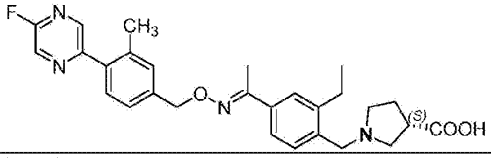
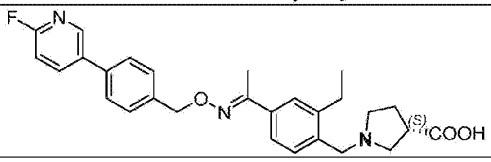
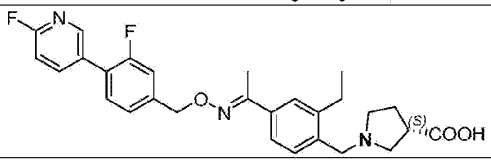
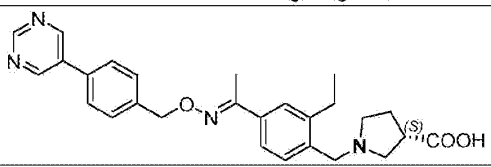
9		455.50±36.20	2352.00±239.04	1426.00±373.84
10		10.30±0.38	261.60±37.30	159.60±4.90
11		5.63±0.15	573.50±106.45	254.80±10.90
12		17.73±3.25	2251.00±701.50	1678.00±455.00
13		5099.00±1511.48	3238.00±1129.35	3111.00±258.91
14		5991.00±830.82	3665.00±387.61	7543.00±901.31
15		806.60±241.09	560.10±184.62	560.50±134.72
16		23.17±10.86	3315.00±863.14	1270.00±456.82
17		2.21±0.58	389.50±195.42	95.57±42.08
18		2.95±0.69	266.40±62.77	63.06±21.76
19		8.63±0.39	563.90±184.36	121.40±30.39

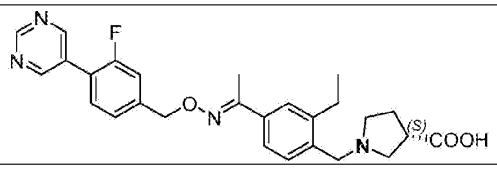
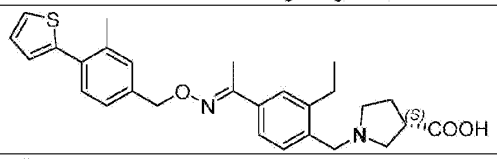
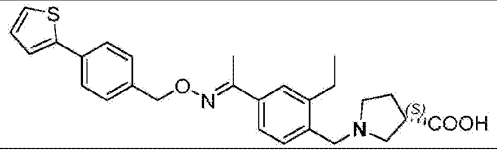
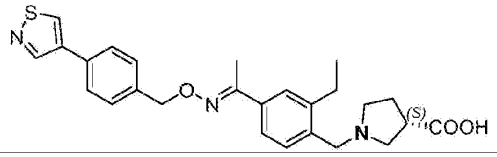
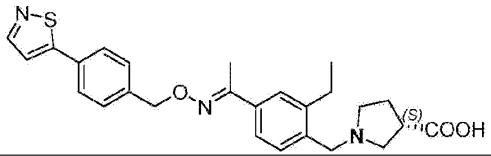
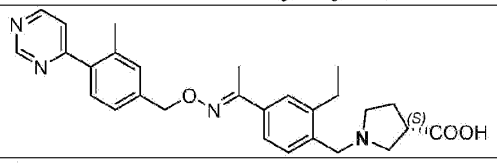
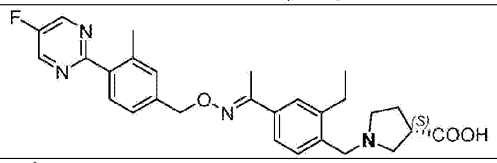
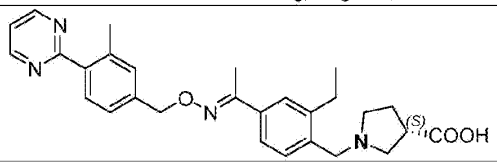
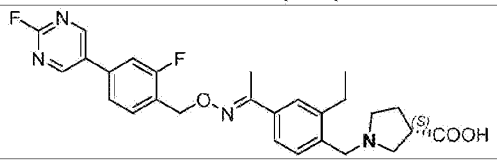
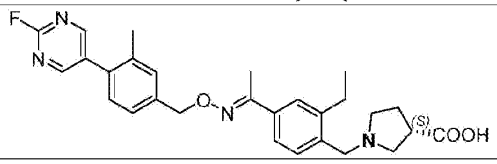
20		781.80±24.90	234.60±54.29	273.10±54.21
21		11.96±0.03	192.20±64.93	70.78±27.07
22		55.47±7.82	114.50±83.50	27.03±6.93
23		560.50±24.80	569.50±157.62	585.90±80.57
24		11.64±2.84	257.10±57.40	219.20±80.40
25		1.06±0.28	269.60±99.60	157.10±55.19
26		0.31±0.02	146.90±30.79	57.40±17.42
27		55.50±3.43	1697.00±588.45	1130.00±74.84
28		99.07±16.20	23.56±7.43	57.19±16.78
29		169.20±32	54.41±0.72	87.17±4.08
30		87.64±3.35	9.09±0.67	14.97±3.78

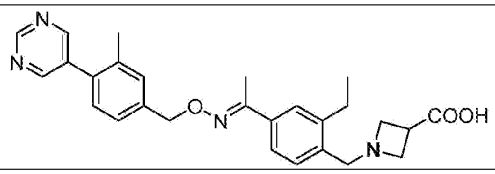
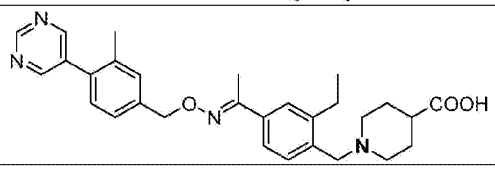
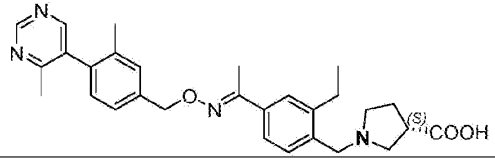
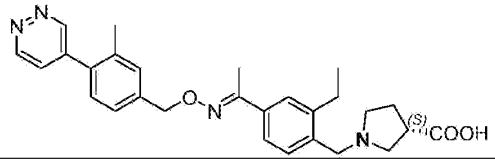
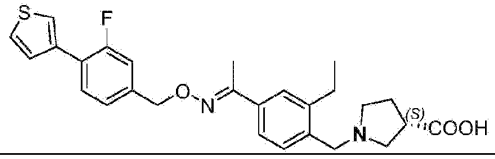
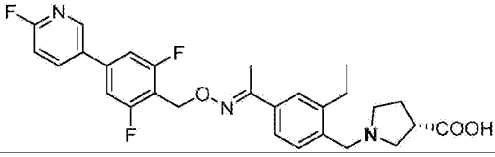
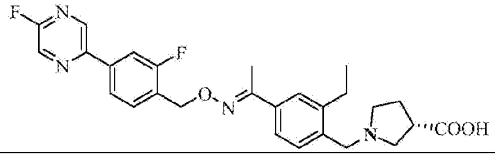
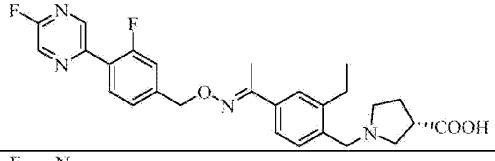
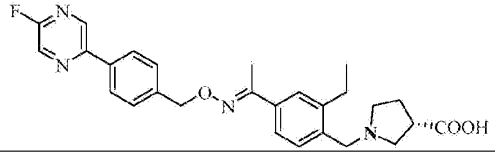
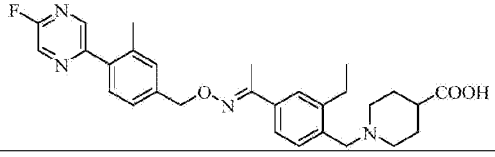
31		128.30±10.00	77.07±3.04	73.10±4.91
32		88.02±3.66	116.00±20.29	110.50±6.85
33		454.20±84.20	127.10±9.85	175.40±36.50
34		86.87	2.405	
35		103.6	3.791	
36		103.3	1.667	
37		643.8	15.59	
38		2974±216.74	13.99±2.39	
39		>10000	311.40±49.28	
40		>10000	73.63±12.88	

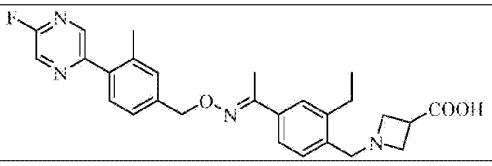
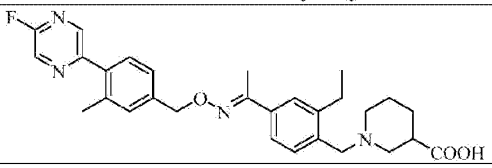
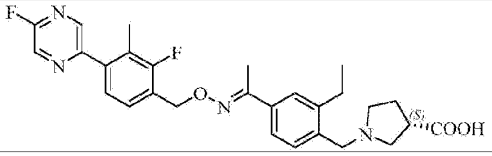
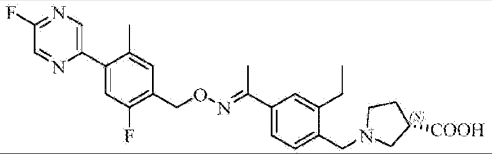
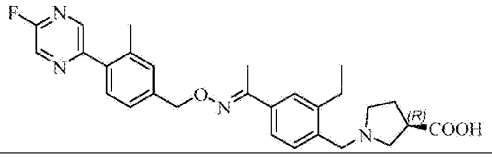
41		51.55±1.82	2.91±0.01	
42		3.825±0.24	20.53±0.98	
43		2092±223.54	55.33±8.32	
44		>10000	878.5±45.87	
45		>10000	407.40±74.54	
46		5606±420.18	487.50±18.97	
47		131.7±4.40	4.67±0.71	
48		**276.4±26.98**	**210.8±100.8**	
49		**66.07±8.58**	**181.3±100.8**	
50		**3365±397.2**	**101.9±97.13**	

51		**195±27.65**	**118±46.21**	
52		**218.8±66.2**	**26.31±3.26**	
53		**238.9±97.56**	**7.02±0.59**	HYY20
54		**765.3±81.76**	**13.53±8.58**	
55		>10000	**268.7**	
56		**686.1±49.07**	**5.05±1.84**	
57		**664.1±119**	**6.52±0.073**	
58		**510.1±250.2**	>10000	.1
59		**86.08±20.7**	**44.25±23.21**	
60		**3.50±1.64**	**71.69**	

61		4.75±1.88	3.33±2.5	
62		1.13±0.3818	3.31±0.24	
63		21.89±1.03	5.86±0.27	
64		239.1±1.63	7.77±1.02	
65		>10000	10.51±0.28	
66		>10000	421.9±10.61	
67		194.8±16.05	1.80±0.43	
68		7536±941.2	33.69±12.04	
69		4981±525.4	8.28±0.38	
70		>10000	36.17±6.58	

71		>10000	34.06±6.08	
72		112.1±0.85	1.51±0.64	
73		1113±55.86	10.68±0.11	
74		>10000	13.13±0.02	
75		>10000	34.17±0.22	
76		549.1±77.78	4.39±0.91	
77		270.9±8.77	5.93±4.12	
78		1888±127.3	215.8±64.91	
79		>10000	444.7±88.81	
80		2082±40.31	18.05±0.52	

81		**2254±23 6.9**	**102.7±9.1**	
82		**>10000**	**42.7±2.28**	
83		**>10000**	**40.95±0.2 2**	
84		**>10000**	**254.1±72. 34**	
85		**173.1±9. 69**	**8.52±0.21**	
86		**>10000**	**42.22±10. 71**	
87		**>10000**	**17.4±0.39**	
88		**3207±11 1.7**	**27.38±1.1 2**	
89		**5250±23 4.8**	**135.2±17. 75**	
90		**5950±72 .83**	**>10000**	

91		54.45±0.20	＞10000	
92		＞10000	＞10000	
93		347.9±40.44	12.03±1.00	
94		613.9±50.25	13.94±1.48	
95		125.0±14.50	75.38±5.72	

[0428] 虽然现在有部分S1PR4调节剂报道，但这些化合物大多机制不明，没有详细的构效关系分析，缺乏体内药代动力学参数，无法评估这些化合物的体内有效性。本发明人以S1PR1/5激动剂BAF312为先导化合物，基于S1PR1和S1PR4的β-arrestin招募活性评价体系，针对BAF312的极性头部，疏水端进行了改造，合成并评价了一系列化合物。通过对化合物BAF312进行充分地S1PR1/4构效关系讨论，本发明人发现将BAF312的环已基更换为苯环，将其三氟甲基更换为甲基合成化合物22后，可以显著降低S1PR1的活性，但可以保持S1PR4的活性。随后，本发明人修饰了化合物22的极性头部区域，发现手性吡咯烷羧酸的引入进一步提高了化合物对S1PR4的活性，因此发现了选择性S1PR4激动剂30。测试结果表明化合物30对S1PR4的β-arrestin招募活性达到EC_{50}＝9.09nM，接下来对优势化合物30进行了S1PR1-5选择性分析，测试结果表明：与内源性配体S1P相比，化合物30对S1PR2/3/5靶点没有体现激动活性，对S1PR1的选择性达到将近10倍，进一步证明了化合物30是选择性S1PR4激动剂，并且对S1PR4的激动活性明显高

于内源性配体S1P。同时化合物67相比化合物30，体现出更优异的S1PR4选择性及活性。化合物67针对S1PR4的活性达到1.80nM,对S1PR1的选择性大于100倍。

[0429] 化合物30、67在S1PRs的选择性

Receptor	EC_{50}/nM (Emax/%) **30**	EC_{50}/nM (Emax/%) **67**	EC_{50}/nM S1P
S1PR1	87.64±3.35 (101.66)[a]	194.8± 16.05 nM[a]	8.52±1.06[a]
S1PR2	>10000 (-6.90)[b]	>10000 nM[a]	2.95±1.37[b]
S1PR3	>10000 (2.25)[c]	>10000 nM[a]	20.60±3.37[c]
S1PR4	9.09±0.67 (103.51)[a]	1.80±0.43 nM[a]	100.00±21.85[a]
S1PR5	>10000 (19.51)[b]	3740±221.3 nM[a]	2.00±1.90[b]

[a]基于Tango-S1PR1-CHO-K1和Tango-S1PR4-CHO-K1细胞的β-restin募集活性，表示

为EC_{50}值的平均值±SD。[b]FLIPR分析基于S1PR2-CHO和S1PR5-CHO细胞系进行，表示为EC_{50}值的平均值±SD。[c]基于PathHunter CHO-K1-S1PR3细胞的β-restin募集活性，表示为EC_{50}值的平均值±SD。数据为至少两次独立测定的平均值，报告为平均值±SD(标准偏差)的形式。

[0430] 实施例3.系列化合物药代动力学性质测试

[0431] 在构效关系讨论中，本发明人得到了关键化合物22，然后在22的基础上，对化合物的极性头部修饰为手性吡咯烷羧酸，得到了选择性S1PR4激动剂30及67。我们对化合物22、30和67分别进行了药代动力学性质分析，发现化合物22保留和BAF312相似的环丁酸极性头部，但是体现出S1PR1和S1PR4双重活性，并且生物利用度仅达到23.5%，成药性不佳。而新发现的化合物30及67，不仅体现出优异的S1PR4激动活性，并且其口服吸收性质优异，体内暴露量大大提高，口服生物利用度分别达到119.7%和76.21%，更加具备成药潜力。

[0432] 化合物22的药代动力学参数[a]

Parameter	Compound **22**	
	IV (1 mg/kg)	PO (10 mg/kg)
Tmax (h)	0.08±0	0.83±0.29
$T_{1/2}$ (h)	0.42±0.03	2.16±0.96
Cmax (ng/mL)	995.32±53.20	544.44±221.09
AUC_{0-t} (h*ng/mL)	475.87±43.64	1118.59±399.59
CL_obs (L/h/kg)	2.08±0.19	8.90±3.86
Vss_obs (L/kg)	0.88±0.07	27.73±16.85
F (%)	--	23.5

[0433] 化合物30的药代动力学参数[a]

Parameter	Compound **30**	
	IV (1 mg/kg)	PO (10 mg/kg)
Tmax (h)	0.08±0	2.00±0
$T_{1/2}$ (h)	2.15±0.06	2.78±0.12
Cmax (ng/mL)	437.70±82.58	1031.52±91.90
AUC_{0-t} (h*ng/mL)	823.51±284.02	9860.13±794.15
CL_obs (L/h/kg)	1.21±0.44	1.02±0.08

Parameter	Compound **30**	
	IV (1 mg/kg)	PO (10 mg/kg)
Vss_obs (L/kg)	3.59±1.16	4.08±0.32
F (%)	--	119.7

[a]利用体重为200−220g的SD大鼠(雄性，每组3只)以供研究。

[0434] 化合物67的药代动力学参数[a]

Parameter	Compound 67	
	IV (1 mg/kg)	PO (10 mg/kg)
Tmax (h)	0.08±0.00	1.83±1.89
$T_{1/2}$ (h)	1.18±0.01	2.17±0.11
Cmax (ng/mL)	958.08±45.87	986.13±277.10
AUC_{0-t} (h*ng/mL)	836.22±26.98	6372.51±1509.83
CL_obs (L/h/kg)	1.19±0.04	1.55±0.27
Vss_obs (L/kg)	1.52±0.02	4.88±1.17
F (%)	--	76.21

[a]利用体重为200−220g的SD大鼠(雄性，每组3只)以供研究。

[0435] 实施例4.内化功能测试

[0436] S1P可以引起受体内化，抑制淋巴细胞从次级淋巴组织流出，从而降低机体组织中的炎症反应，这也是S1P靶点药物可以治疗疾病的关键生物作用。因此进行化合物30对S1PR4内化后受体的恢复程度评价，在S1PR4高表达的细胞中评价了化合物30引起受体内化后的恢复作用。用1μM浓度的S1P、BAF312和化合物30处理S1PR4−293T细胞，在37℃下持续1.5小时，随后立即或间隔5小时或20小时检测细胞表面的S1PR4受体表达情况。如图1所示，BAF312作为S1PR1和S1PR5激动剂，由于不具备S1PR4的激动活性，所以不能引起S1PR4受体内化。S1P可以引起S1PR4内化，并且在20小时后受体表达恢复，选择性S1PR4激动剂30对S1PR4有长达20小时的持续内化能力，证明化合物30是较强的选择性S1PR4激动剂。化合物30诱导S1PR4内化后的恢复效果如图1所示。

[0437] 实施例5.化合物30在系统性红斑狼疮(SLE)体内药效测试

[0438] 系统性红斑狼疮(SLE)，是典型的自身免疫疾病，累及多器官、多组织，主要特征为产生多种特异性自身抗体、免疫系统异常激活，常伴随凝血、纤溶异常，多发于中青年女性，我国发病率近70/10万人。SLE病因和发病机理尚未完全明确，现有研究提示发病机制与基因、激素、环境等综合因素的共同作用诱导机体抗原累积、自身抗体产生、免疫过度活化，打破免疫平衡，自身耐受功能发生障碍，从而导致器官损伤、发生炎症反应，并伴随着免疫细胞异常有关。T、

B淋巴细胞高度活化被认为是自身免疫性疾病发病的关键因素，活化的T淋巴细胞分泌相关的细胞因子反作用于B淋巴细胞，使其增殖分化产生自身抗体，形成免疫复合物，沉积到机体各处器官、组织，造成机体炎症反应，使免疫系统功能紊乱。

[0439] 肾脏是SLE最常见的受累器官，称为狼疮性肾炎，肾脏发生毛细血管、系膜细胞和基质增生，炎性细胞浸润，免疫复合物沉积等，进而导致肾间质纤维化，和肾小球硬化，肾功能异常。

[0440] SLE尚无有效根治药物，目前临床SLE的治疗仍然是大剂量的糖皮质激素，虽可一定程度控制疾病的进展，但无法根治，且长期服药容易使机体产生耐药性，药物的不良反应较严重，常见的并发症会严重影响SLE患者的生活质量。

[0441] 本发明人设计合成的S1PR4激动剂化合物30对多种炎症和免疫相关疾病均表现出很好的疗效。在此基础上，本发明人采用红斑狼疮MRL/lpr模型小鼠对该化合物进行了药效评价，结果显示，8周后SLE模型组小鼠体重明显增高(提示肾功能损伤)，并出现小鼠死亡。化合物30连续给药8个星期可阻止动物体重增加，并剂量依赖性降低动物死亡率，作用优于泼尼松龙(如图2所示)。

[0442] 对SLE表型研究显示，化合物30可显著减少SLE小鼠皮下结节，并可在治疗一段时间后使结节消失，明显降低血清抗核抗体dsDNA的水平，作用优于泼尼松龙，并显示较好的剂量依赖性(如图3所示)。

[0443] 免疫学研究显示，SLE小鼠脾脏Th1、Th17细胞数量显著高于正常对照组，化合物30可显著降低Th1和Th17阳性细胞数，Th1/Th2和Th17/Treg比值，提示其治疗作用与调节T淋巴细胞的数量及功能有关(如图4所示)。

[0444] 鉴于狼疮性肾炎为SLE最常受损的器官，本发明人分别对各组小鼠的肾脏进行了HE和PAS染色。结果显示SLE小鼠有严重的肾间质炎性细胞浸润，并出现系膜细胞增生和基底膜增厚；化合物30治疗8周后肾间质炎性细胞浸润显著减少，并可减轻系膜细胞增生和基底膜增厚的病理变化，且效果优于泼尼松龙(如图5所示)。

[0445] 综上所述，化合物30对SLE有很好的药效，且疗效优于阳性药泼尼松龙。作为S1PR4选择性激动剂，化合物30的靶标及作用机理均不同于目前临床应用的治疗

药物，是全新靶点的免疫调节剂，有望成为新靶标、新机制治疗红斑狼疮的药物。

[0446] 实施例6.化合物30对急/慢性溃疡性结肠炎小鼠的药效评估

[0447] UC是一种肠道炎症性疾病(inflammatory bowel disease，IBD)，常见于30至40岁的成年人。该病主要从直肠开始产生，并延伸到乙状结肠，易复发。临床表现主要包括腹泻、腹痛、黏液血便等，病理特征主要为炎症细胞浸润、溃疡，严重时可导致结肠癌的发生。

[0448] 溃疡性结肠炎病因和发病机制仍不清楚，持续肠道感染、肠黏膜屏障缺损、肠黏膜免疫调节异常、遗传和环境等因素共同参与了疾病发生过程。免疫因素被公认是IBD发病机制中极为重要的一个因素。肠上皮作为屏障的重要组成部分，在免疫防御和免疫活化之间起着重要的枢纽作用，通过各种机制维持黏膜稳态进而保护宿主。正常生理情况下，上皮细胞、免疫细胞和间质细胞之间的分子通信维持上皮细胞再生和黏膜愈合。多种类型的细胞，包括抗原提呈细胞、辅助性T细胞、调节性T细胞和自然杀伤T细胞，通过调节、维持或抑制炎症在UC发病中发挥着至关重要的作用。

[0449] UC治疗的常用药物有5-氨基水杨酸、糖皮质激素和免疫抑制剂，虽然这些药物能有效减轻疾病活动，但都有各自的局限性和潜在的并发症，例如糖皮质激素有严重的副反应和广泛的禁忌症，不适用于长期使用，而生物制剂存在诱发感染和促肿瘤的风险。另外，近年来随着UC的发病率升高，部分患者出现对传统药物治疗应答不佳或无应答，导致病情迁延、长期反复发作，这促使人们努力开发新的治疗方式和方法，免疫抑制剂及生物制剂治疗是目前关注重点。通过构建急性和慢性溃疡性结肠炎小鼠模型，本发明人评价了S1PR4激动剂化合物30在该疾病中的治疗效果，具体实验方法和结果如下所示。

[0450] 1.实验方法

[0451] 1.1急性溃疡性结肠炎

[0452] 实验Day0-Day14每天称重并观察小鼠的血、便情况，按下表(表1)打分并记录。Day1随机分组，Day1-Day7造模，除Control组其余每组每天给与3.5%DSS水，Day8重新分组。Control组和Model组不给药，给与自来水；其余组分别给与

30 1mg/kg、3mg/kg、9mg/kg、SASP(柳氮磺吡啶或水杨酰偶氮磺胺吡啶)500mg/kg，灌胃给药。Day15取血、取结肠，测量结肠长度，并用甲醛固定1～2cm的结肠。

[0453] 1.2慢性溃疡性结肠炎

[0454] BALB/c小鼠实验前7天适应性饲养，实验Day7-Day50每天称重并观察小鼠的血、便情况，按下表(表1)打分并记录。随机分组后，除Control组，其余组均于Day7-Day14给与动物2～3%DSS溶液自由饮造模，Day7-Day14正常饮水。14天为一次循环，重复3次，且于最后一次循环开始时重新分组，开始给药；Control组和Model组不给药，给与相同溶剂；其余组分别给与30 1mg/kg、3mg/kg、9mg/kg、SASP 500mg/kg，灌胃给药。Day45取血、取结肠，测量结肠长度，并用甲醛固定1～2cm的结肠。

[0455] 2.实验材料包括：

[0456] BALB/c小鼠，雄性，20-22g

[0457] 葡聚糖硫酸钠盐MW：36000～50000(DSS)

[0458] 30 1mg/kg、3mg/kg、9mg/kg、SASP(500mg/kg)观察指标

[0459] 3.治疗效果

[0460] 3.1药效

[0461] (1)临床症状评分：实验期间每天称重并观察小鼠的血、便情况，进行DAI评分，按下表(表1)打分并记录。

DAI 评分					
直肠出血		粪便稠度		体重减轻	
0	正常	0	正常，松散便	0	无
1	轻微出血	1	软便	1	1%~4.99%
2	血	2	稀糊便	2	5%~10
3	大量出血	3	水性腹泻	3	>10%

[0462] (2)实验结束取结肠，测量结肠长度，并称重，计算结肠体重指数(结肠重量/体重×100%)、结肠肿胀率(结肠重量/长度×100%)

[0463] 3.2病理形态变化

[0464] 取距肛门边缘0.5cm约1cm的结肠组织，取回盲区进行组织病理学检查。H&E染色后，在单盲条件下对组织进行评分，以评估结肠远端炎症和组织损伤水平；评分是根据Ameho标准，并计算如下：

[0465] 0分：纹理没有异常发现；

[0466] 1分：黏膜和/或黏膜轻度炎性浸润(混合中性粒细胞)，下层水肿，黏膜点状糜烂，伴有毛细血管增生。粘膜肌层是完整的；

[0467] 2分：1点变化占50％以上；

[0468] 3分：炎性浸润和水肿明显，(中性粒细胞往往占主导地位)；通常溃疡穿透黏膜肌层到达黏膜下层。固有肌层几乎没有炎性细胞浸润，也没有肌肉坏死；

[0469] 4分：3点变化占比超过50％；

[0470] 5分：大片状溃疡伴凝固性坏死，边缘有大量中性粒细胞浸润，单核细胞较少。坏死组织穿透固有肌层；

[0471] 6分：5点的变化占标本的50％以上；

[0472] 3.3结肠黏膜屏障变化

[0473] Occludin的栅栏功能可将上皮细胞质膜顶侧和基测隔开，限制细胞膜上的脂质自由流动，有利于形成细胞极性，维持肠黏膜的不可通透性及硬度，防止病原微生物的进入，Occludin的屏障功能则可以调节小分子的运输，维持组织稳态。通过免疫组化检测相关蛋白的表达与分布；

[0474] 4.实验结果

[0475] 4.1化合物30对DSS诱导的急性溃疡性结肠炎小鼠的药效观察

[0476] 本次实验造模7天后，重新分组，每组8只小鼠，从第8天开始，陆续有小鼠死亡。其中，Control组未出现死亡；模型组死亡2只，生存率75％；阳性药SASP组死亡1只，生存率87.5％；30 1mg/kg组死亡1只，生存率87.5％；30 3mg/kg组死亡1只，生存率87.5％；30 9mg/kg组死亡2只，生存率75％；与模型组相比，阳性药SASP和30给药均可提高UC模型小鼠的生存率。给药化合物30的急性UC模型小鼠生存曲线如图6所示。

[0477] 4.2化合物30对急性UC模型小鼠体重和DAI评分的影响

[0478] 体重：本次实验造模第4天，小鼠体重开始普遍下降，第8天体重普遍降低至最低点，之后体重开始回升；图7显示，与control组相比，其他组体重明显下降，说明造模成功；与model组相比，SASP、30-3mg/kg给药组体重恢复较快，且体重回升幅度较大；

[0479] DAI评分：DAI(疾病活动指数)随着造模时间的增加，评分逐渐增加，停止造模后评分逐渐下降。与model组相比，SASP、30给药组DAI评分下降较快(如图8所示)；

[0480] 将14天的DAI进行总和(如图9所示)，与model组相比，30 3mg/kg给药组存在显著性降低；说明30 3mg/kg可以改善DSS引起的小鼠体重下降、便血、腹泻等症状。

[0481] 4.3化合物30对急性UC模型小鼠结肠长度、重量及肿胀率影响

[0482] UC患者和小鼠模型通常会出现结肠缩短的现象。图10显示，与Control组相比，Model组小鼠的结肠长度明显缩短(*p<0.05)，30 1mg/kg、3mg/kg显著抑制了DSS引起的结肠变短30 1mg/kg，*p<0.05；30 3mg/kg，**p<0.01,vs.Model group)，与疾病活动指数结果基本一致。图11为结肠重量图，但统计学上无显著差异，为排除结肠变长而导致的重量增加这一因素，使用结肠重量与长度的比值来代表结肠的肿胀程度，结果如图12所示，与Control组相比，Model组的结肠重量与长度的比值显著增加。

[0483] 4.4病理形态变化

[0484] 组织病理学检查是临床确诊UC的重要手段，为进一步确证30对UC的作用，我们用PFA固定结肠后进行石蜡切片，H&E染色观察结果。H&E染色中的苏木精染液呈碱性，可将核内染色质和胞质内核酸染成紫蓝色：伊红染液为酸性，可将胞质及细胞外基质染为红色。通过H&E染色可观察到组织中的结构改变、炎症情况、脓肿等UC的病理特点。结果如图13所示，Control组小鼠结肠黏膜结构完整，肠上皮完整，可见大量杯状细胞且排列有序，未见炎症细胞浸润。DSS造模后，模型组小鼠的结肠黏膜固有层、黏膜下出现了明显的炎症细胞浸润，并浸润至肌层，杯状细胞也明显减少，黏膜变薄，黏膜上皮细胞丢失，表明造模成功。阳性药SASP组虽有炎症细胞浸润，但程度不及Model组，且杯状细胞多于

Model组，排列也较整齐。30 9mg/kg组可见明显的炎症细胞浸润、杯状细胞减少。化合物30 1mg/kg、3mg/kg给药后，黏膜结构正常，杯状细胞增多且排列整齐，未见明显的炎症细胞浸润，且上皮细胞丢失的情况也得到了改善。图14为各组病理评分结果。因此，总体来看，与Model组相比，SASP、化合物30对结肠黏膜损伤都有一定的改善作用，但化合物30 1mg/kg、3mg/kg保护效果要优于其他组。

[0485] 结肠黏膜屏障变化

[0486] 结肠黏膜屏障是肠道最有效的一道屏障，结肠上皮细胞通过黏附分子相互黏附，并黏附在细胞外基质上。结肠上皮细胞间可以通过紧密连接(TJs)、黏附连接、缝隙连接等方式连接在一起，其中，TJs是最重要的连接方式。TJs的功能有两种：首先是，选择性屏障功能，可以帮助维持肠上皮的选择性通透性，只允许离子和小分子可溶性物质通过；其次是维持栅栏功能。这一特殊的生理功能使结肠黏膜除了可以吸收细胞新陈代谢所需的水、营养物质和分子外，还可以阻止细菌和抗原从肠腔入侵。TJs蛋白处于细胞-细胞连接复合体的最上方，它的表达和分布的改变可以通过调节结肠黏膜内稳态和肠道通透性来改变结肠的炎症水平。DSS会导致小鼠结肠屏障受损，但具体机制未明，可能是DSS的细胞毒性导致结肠上皮中的TJs受到破坏，TJs在结肠黏膜的位置也被改变，使细菌更容易渗透进肠组织并产生炎症。咬合蛋白Occludin是其中重要的TJ蛋白。因此，使用免疫组化的方法来检测相关蛋白表达。

[0487] Occludin的栅栏功能可将上皮细胞质膜顶侧和基测隔开，限制细胞膜上的脂质自由流动，有利于形成细胞极性，维持肠黏膜的不可通透性及硬度，防止病原微生物的进入，Occludin的屏障功能则可以调节小分子的运输，维持组织稳态。

[0488] 通过免疫组化测定结肠黏膜中Occludin的表达，结果如图15所示。与Control组相比，Model组Occludin的表达减少，表明DSS造模后，小鼠肠道屏障受损。SASP、化合物30处理后，Occludin的表达增多。图16使用蛋白免疫印迹法检测结肠中Occludin蛋自的表达，与Model组相比，化合物30可以增加Occludin的表达，与免疫组化结果基本一致。

[0489] 化合物30对DSS诱导的慢性溃疡性结肠炎小鼠的药效观察

[0490] 5.1化合物30对慢性溃疡性结肠炎小鼠体重的影响

[0491] 造模期间，control组小鼠体重均稳定上升；model组第一次造模期间给与3%dss自由饮7日，自来水自由饮7日。造模第4天，小鼠体重开始普遍下降，第8天体重普遍降低至最低点，之后体重开始回升；第二次造模期间给与2%dss自由饮7日，自来水自由饮7日。给DSS 7天期间小鼠体重不再增加，相比于对照组有明显降低，给水之后体重开始回升；第三次造模前，根据模型组小鼠体重以及DAI评分均匀分为model、sasp-500mg/kg、30-1mg/kg、30-3mg/kg、30-9mg/kg组，每组11只；给与2.75%dss自由饮7日，自来水自由饮7日。给药组相较于model组，体重下降较轻，恢复饮水后体重回升较快；

[0492] 与control组相比，其他组体重明显下降，说明造模成功；与model组相比，SASP、30给药组体重恢复较快，且体重回升幅度较大；其中30-1mg/kg、30-3mg/kg给药期间小鼠体重较为稳定；

[0493] 其中model相较于control组体重变化率有显著降低，给药组一定程度上抑制了模型小鼠的体重下降，其中30-3mg/kg给药组相较于model组体重变化率存在显著上升。造模期间各组体重变化如图17所示；开始给药后各组体重变化如图18所示；给药前后各组体重变化率如图19所示。

[0494] 5.2化合物30对慢性UC模型小鼠DAI评分的影响

[0495] DAI评分：DAI(疾病活动指数)随着造模时间的增加，评分逐渐增加，停止造模后评分逐渐下降。与model组相比，SASP、30给药组DAI评分下降较快；

[0496] 将给药14天的DAI进行总和，与model组相比，30 3mg/kg给药组存在显著性降低；说明30 3mg/kg可以改善DSS引起的小鼠体重下降、便血、腹泻等症状。

[0497] 造模期间慢性UC模型每日DAI评分如图20所示；给药期间慢性UC模型每日DAI评分如图21所示；给药期间各组慢性UC模型每日DAI评分总和如图22所示。

[0498] 5.3化合物30对慢性UC模型小鼠结肠长度、重量及肿胀率影响

[0499] UC患者和小鼠模型通常会出现结肠缩短的现象，图23中，与Control组相比，Model组小鼠的结肠长度明显缩短，化合物30 3mg/kg、9mg/kg显著抑制了DSS引起的结肠变短。图24为结肠重量图，为排除结肠变长而导致的重量增加这一因

素，使用结肠重量与长度的比值来代表结肠的肿胀程度，结果如图25所示，与Control组相比，Model组的结肠重量与长度的比值显著增加；

[0500] 5.4病理形态变化

[0501] 组织病理学检查是临床确诊UC的重要手段，为进一步确证30对UC的作用，本发明人用PFA固定结肠后进行石蜡切片，H&E染色观察结果。H&E染色中的苏木精染液呈碱性，可将核内染色质和胞质内核酸染成紫蓝色：伊红染液为酸性，可将胞质及细胞外基质染为红色。通过H&E染色可观察到组织中的结构改变、炎症情况、脓肿等UC的病理特点。

[0502] 结果如图26所示，Control组小鼠结肠黏膜结构完整，肠上皮完整，可见大量杯状细胞且排列有序，未见炎症细胞浸润。慢性DSS造模后，模型组小鼠的结肠黏膜固有层、黏膜下出现了明显的炎症细胞浸润，并浸润至肌层，杯状细胞也明显减少，黏膜变薄，黏膜上皮细胞丢失，表明造模成功。阳性药SASP组虽有炎症细胞浸润，但程度不及Model组，且杯状细胞多于Model组，排列也较整齐。30 1mg/kg、3mg/kg给药后，黏膜结构正常，杯状细胞增多且排列整齐，未见明显的炎症细胞浸润，且上皮细胞丢失的情况也得到了改善。图27为各组病理评分结果。因此，总体来看，与Model组相比，SASP、30对结肠黏膜损伤都有一定的改善作用，但30 1mg/kg、3mg/kg保护效果要优于其他组。

[0503] 结肠黏膜屏障变化

[0504] 结肠黏膜屏障是肠道最有效的一道屏障，结肠上皮细胞通过黏附分子相互黏附，并黏附在细胞外基质上。结肠上皮细胞间可以通过紧密连接(TJs)、黏附连接、缝隙连接等方式连接在一起，其中，TJs是最重要的连接方式。TJs的功能有两种：首先是，选择性屏障功能，可以帮助维持肠上皮的选择性通透性，只允许离子和小分子可溶性物质通过；其次是维持栅栏功能。这一特殊的生理功能使结肠黏膜除了可以吸收细胞新陈代谢所需的水、营养物质和分子外，还可以阻止细菌和抗原从肠腔入侵。TJs蛋白处于细胞-细胞连接复合体的最上方，它的表达和分布的改变可以通过调节结肠黏膜内稳态和肠道通透性来改变结肠的炎症水平。DSS会导致小鼠结肠屏障受损，但具体机制未明，可能是DSS的细胞毒性导致结肠上皮中的TJs受到破坏，TJs在结肠黏膜的位置也被改变，使细菌更容

易渗透进肠组织并产生炎症。咬合蛋白Occludin是其中重要的TJ蛋白。因此，使用免疫组化的方法来检测相关蛋白表达。

[0505] Occludin的栅栏功能可将上皮细胞质膜顶侧和基测隔开，限制细胞膜上的脂质自由流动，有利于形成细胞极性，维持肠黏膜的不可通透性及硬度，防止病原微生物的进入，Occludin的屏障功能则可以调节小分子的运输，维持组织稳态。

[0506] 通过免疫组化测定结肠黏膜中Occludin的表达，结果如图28和29所示。与Control组相比，Model组Occludin的表达减少，表明DSS造模后，小鼠肠道屏障受损。SASP、30处理后，Occludin的表达增多。

[0507] 实施例7.化合物30/38/53/67/77/80在小鼠急性UC模型中的药效

[0508] 除了化合物30，本发明人进一步评估了其他几个S1PR4化合物38、53、67、77、80，进一步证明S1PR4激动剂治疗溃疡性结肠炎的应用潜力。

[0509] 使用DSS进行小鼠造模，方法为2.5%DSS饮水5天+自由饮水2天。造模的同时进行灌胃给药，RPC1063作为阳性药。分组情况具体是：RPC1063灌胃给药1mg/kg。化合物30给药剂量分别是0.3mg/kg，1mg/kg，3mg/kg三组。化合物38是5mg/kg，化合物53是1mg/kg，化合物67是1mg/kg，化合物77是1mg/kg，化合物80是1mg/kg。

[0510] 实验结果(如图30所示)显示67体重下降程度较轻，30恢复情况存在浓度依赖性。DAI评分显示化合物30和67效果较好。在结肠长度方面，其中30，67效果较好，阳性药无明显效果。

[0511] 实施例8.化合物30在大鼠骨关节炎(OA)模型中的药效

[0512] 一.动物和主要试剂：

[0513] 实验动物：

[0514] SD大鼠，200g左右，雄性。购于上海必凯动物有限公司。适应性饲养7天左右。

[0515] 实验药物：化合物30。

[0516] 二.实验分组：

组号	分组	大鼠数量
1	Control	10
2	Model	10
3	双氯芬酸钠 2.5mg/kg	10
4	化合物 30 0.3mg/kg	10
5	化合物 **30** 1mg/kg	10
6	化合物 **30** 3mg/kg	10

[0517] 三.实验方案：

[0518] 3.1.造模方法：

[0519] 3.1.1.麻醉：将大鼠放入麻醉盒内，打开O2气源、气体输送泵，旋转气体调节旋钮，使O2和异氟烷气体比例为8：2。调节麻醉深度旋钮，首先将指针指到3，对大鼠进行深度麻醉；后续手术过程中，调整指针至1.5，维持麻醉。打开三通阀门，使气体输送进入麻醉盒和大鼠麻醉面罩内。

[0520] 3.1.2.进针：使用75％乙醇对大鼠右侧膝盖部位皮肤进行消毒，使其弯曲90° ，用手轻触大鼠膝关节找出髌骨，在髌骨下缘慢慢向关节内测摸索出胫骨平台的位置，将注射器针尖与平台呈45° 角沿髌韧带外侧进针，如下图所示。Control组注射50μl的0.9％无菌生理盐水，其余各组注射50μl内含3mg的MIA无菌生理盐水。操作完成后，取下大鼠，放入饲养笼，用白炽灯照射帮助大鼠恢复体温，直至大鼠从麻醉状态中苏醒。

[0521] 3.2.药物配制：

[0522] Control组给予5％DMSO+35％PEG400+60％生理盐水，化合物溶于5％的二甲基亚砜(Dimethyl Sulfoxide,DMSO)，35％的聚乙二醇400(Polyethylene Glycol 400,PEG 400)以及60％的生理盐水体系中，药物溶液为给药前一天晚配制。

[0523] 3.3.给药

[0524] 大鼠适应性生长1周，随机分组，共10只。Control组给予5％DMSO+35％PEG400+60％生理盐水，其余各组给予待测化合物，溶剂为5％的DMSO+35％PEG400+60％生理盐水。

[0525] 3.4.实验流程：如上图31所示。

[0526] 3.4.1.大鼠从实验第1天至实验第14天，每天灌胃给药一次，灌胃体积为5mL/kg。Control组和Model组在整个实验期间给予5%DMSO+35%PEG400+60%生理盐水，其余各组给予相应的药物。

[0527] 3.4.2.OA疾病活动指数评分

[0528] 实验第7天和第14天对大鼠进行行为学及关节疼痛检测。为减少干扰因素，检测时间固定在给药后1h，防止不同时间段大鼠的状态不同而影响实验结果；实验开始前需让大鼠适应环境20min。

[0529] (1)五分钟行走距离和站立次数观察：对树脂盒子的尺寸进行测量，制作相应大小的纸片，在纸片上画上1cm×1cm大小的格子。用透明胶带将纸片封好，防止纸片因大鼠排泄物而破损。随后将画有1cm×1cm大小格子的纸片置于透明树脂盒子中，保证底部平坦。用摄像仪器记录下大鼠5min内的行走过程及轨迹，计数大鼠行走的距离和站立次数。

[0530] (2)关节疼痛检测：固定大鼠待其情绪稳定后轻柔地弯曲大鼠膝关节，若大鼠无反应记为0分；若大鼠短促明显地缩退、嘶叫则评为1分。用缩腿和嘶叫的评分反映大鼠的膝关节疼痛程度。每隔5s进行一次关节疼痛检测，共5次。

[0531] 3.4.3.组织采集

[0532] 实验第15天，麻醉大鼠并摘取其眼球血。血清4℃静置过夜。4℃、3600rpm离心15min。吸取血清保存于—80℃。将大鼠脱颈处死，在冰上沿膝关节剪开，去除皮毛、肌肉等组织。每组取5只，剥离两侧膝关节，观察股骨髁面的色泽、粗糙及完整程度。随后取其膝关节软骨冻存于—80℃。将剩余5只大鼠关节标本置于甲醛固定液中固定。

[0533] 3.4.4.番红-固绿染色

[0534] 本发明人利用番红-固绿染色及OARSI评分对OA模型大鼠膝关节病理变化情况进行进一步的评价。番红呈碱性，能与酸性的蛋白多糖结合，将软骨基质染成红色；固绿呈酸性，而胶原纤维富含的氨基酸呈碱性，所以固绿可将浅表层软骨以及软骨下骨染成绿色。软骨中的蛋白多糖会在软骨受损后释放出来，导致均匀分散的基质排列散乱，番红失染，因此番红可间接反映基质中蛋白多糖的含量。

[0535] 3.4.5.OARIS评分

[0536] 显微镜下观察大鼠膝关节内的病变情况。使用OARIS骨关节炎软骨组织病理学评估系统(OOCHAS)分级评分系统(分级＝6级，评分＝0～24)评估软骨损伤的严重程度(见表)，以判断药物是否可缓解骨关节炎的严重程度。

分级	主要特征	亚级（可不评）	相关标准（组织反应）
0	关节表面完整 软骨完整	无	各组织完整，软骨不受累
1	表面完整	1.0 细胞完整	基质：表层完整、肿胀或纤维化
		1.5 细胞坏死	细胞：增殖成簇、增生肥大
2	表面不连续	2.0 纤维化超过软骨表面	同上
		2.5 软骨面磨损伴表层基质丢失	伴表层不完整； 伴或不伴有基质阳离子染色（番红 O 或甲苯胺蓝染色） 软骨上 1/3（即深达软骨中间层）着色变浅；
3	垂直裂隙	3.0 简单裂隙	同上
		3.5 复杂或分叉裂隙	伴或不伴有基质阳离子染色（番红 O 或甲苯胺蓝染色） 软骨下（即深达软骨中间层）着色变浅；
4	糜烂	4.0 表层分层	软骨基质丢失，基质内囊肿形成
		4.5 中间层囊变	
5	缺损	5.0 骨面完整	骨面硬化或出现包括纤维软骨在内的修复组织
		5.5 出现修复组织	
6	变形	6.0 关节边缘骨赘形成	骨重塑：关节表面形状改变（不只是骨赘形成），包括：微骨析和出现修复组织
		6.5 关节边缘及中心骨赘形成	

分期	损伤占样本的百分比（表面、区域和体积）（%）
0	无骨关节炎表现
1	＜10
2	10-25
3	25-50
4	＞50

分级	分期			
	S1	S2	S3	S4
G1	1	2	3	4
G2	2	4	6	8
G3	3	6	9	12
G4	4	8	12	16
G5	5	10	15	20
G6	6	12	18	24

[0537] 4.实验结果：

[0538] 4.1.造模前大鼠进食饮水正常，毛色光亮。MIA注射造模后，在进行OA造模时,关节 腔注射MIA的大鼠膝关节从进针处开始出现肿胀,肿胀现象随时间逐渐蔓延到整个膝关节,关节出现红肿热痛,大鼠行动减少,左后肢屈缩、跛行,精神萎靡。随着时间的延长，肿胀程度减小。

[0539] 4.2.疼痛指数：

[0540] DAY7，与Model组相比，双氯芬酸钠-2.5mg/kg、化合物30-0.3mg/kg、化合物30-3mg/kg治疗组大鼠的疼痛指数与Model组相比均显著降低。

[0541] DAY14，与Mode组相比，化合物30-1mg/kg、化合物30-3mg/kg治疗组大鼠的疼痛指数与Model组相比均显著降低。

[0542] 疼痛指数统计如图32所示。

[0543] 4.3.五分钟行走距离和直立次数：

[0544] DAY7，与Model组相比，双氯芬酸钠-2.5mg/kg、化合物30-0.3mg/kg、化合物30-1mg/kg治疗组大鼠的行走距离显著上升。

[0545] DAY14，与Model组相比，化合物30-0.3mg/kg、化合物30-3mg/kg治疗组大鼠的行走距离显著上升。5分钟行走距离统计如图33所示。

[0546] DAY7及DAY14，与Model组相比，与Model组相比，直立次数无统计学差异。5分钟直立次数统计如图34所示。

[0547] 4.4.每组取5只处死后，解剖膝关节将大鼠股骨踝暴露，拍摄并观察。我们对大鼠膝关节股骨髁面的色泽、粗糙及完整程度进行总体观察，结果如图35所示：

[0548] Control组大鼠的关节腔滑囊无增生情况，软骨表面光滑完整、色泽鲜亮、无纹裂；关节边缘也没有形成骨赘。

[0549] 而Model组可以看到大鼠关节软骨面略微粗糙，部分糜烂，有小的裂隙且色泽灰暗；关节软骨色泽丢失，表面发生虫蚀改变，边缘有骨赘形成。

[0550] 经过双氯芬酸钠和化合物30治疗后，大部分大鼠膝关节的软骨光滑鲜亮、磨损的情况显著改善。虽然也能看到部分软骨出现了轻微虫蚀的情况，但未见明显的骨赘形成。因此，可以认为化合物30可以缓解OA模型鼠膝关节软骨病变的情况。

[0551] 4.5.化合物30对OA大鼠膝关节番红固绿染色及OARSI评分的影响

[0552] 从图36可以看出，Control组软骨基质颜色红亮；浅层软骨和软骨下骨被固绿染成绿色。软骨结构完整，表层和中层分别为扁平状和圆形圆形的软骨细胞、深层可见软骨细胞增生。而Model组有少量番红染色褪去，局部失染；表层软骨细胞变得肿胀、数量减少、排列紊乱；潮线不规则延申、边界模糊、部分消失。

[0553] 经双氯芬酸钠和化合物30治疗后，OA模型鼠的膝骨关节有所改善，番红染色增强；软骨细胞增多、排列较规则整齐。

[0554] 接下来本发明人用OARIS评分对各组大鼠的骨关节炎严重程度进行了判断，结果如图36所示，Model组的评分比Control组显著升高，而经双氯芬酸钠和化合物30治疗后，大鼠膝骨关节炎较Model组明显要轻。化合物30-0.3mg/kg、化合物30-1mg/kg、化合物30-3mg/kg治疗组大鼠具有显著性，能够很好的缓解OA大鼠膝关节部位的损伤。说明化合物30可以延缓OA的进展。

[0555] 实验结果：

[0556] 本发明人利用膝关节腔内注射MIA来建立大鼠OA模型，研究化合物30对该模型大鼠的药效。发现化合物30可以改善关节损伤大鼠的行走运动能力，减缓大鼠的疼痛感。观察病变部位时，发现化合物30可以改善OA大鼠膝关节软骨磨损、侵蚀、断裂的现象。

[0557] 结论：

[0558] (1)实验结果说明化合物30治疗组大鼠的行走距离显著上升。在MIA诱导的大鼠OA模型中表现出良好的治疗效果，可以有效缓解大鼠的疼痛，改善其行走状态。

[0559] (2)大体观察结果表明，化合物30治疗组大鼠能够很好的缓解OA大鼠膝关节部位的损伤。

[0560] (3)病理切片及OARSI评分的结果表明，化合物30治疗组能够很好的缓解OA大鼠膝关节部位的损伤。

[0561] 实施例9.化合物67在大鼠骨关节炎(OA)模型中的药效

[0562] 大鼠适应性生长1周，随机分组，每组各10只。使用单碘乙酸(MIA)诱导造模。Control组给予5％DMSO+35％PEG400+60％生理盐水，其余各组给予待测化合物，溶剂为5％的DMSO+35％PEG400+60％生理盐水。药物组具体分组情况如下，双氯芬酸钠2.5mg/kg作为阳性对照组。化合物67分为3个剂量组分别是0.3mg/kg，1mg/kg和3mg/kg。

[0563] 造模前大鼠进食饮水正常，毛色光亮。MIA注射造模后，在进行OA造模时,关节腔注射MIA的大鼠膝关节从进针处开始出现肿胀,肿胀现象随时间逐渐蔓延到整个膝关节,关节出现红肿热痛,大鼠行动减少,左后肢屈缩、跛行,精神萎靡。随着时间的延长，肿胀程度减小。

[0564] 化合物67的疼痛指数如图37所示。

[0565] DAY7，与Model组相比，双氯芬酸钠-2.5mg/kg、化合物67-0.3mg/kg、化合物67-1mg/kg、化合物67-3mg/kg治疗组大鼠的疼痛指数与Model组相比均显著降低。

[0566] DAY14，与Mode组相比，化合物67-1mg/kg、化合物67-3mg/kg治疗组大鼠的疼痛指数与Model组相比均显著降低。

[0567] 五分钟行走距离和直立次数如图38和39所示：

[0568] 大鼠五分钟行走距离实验结果显示：DAY7，与Model组相比，双氯芬酸钠-2.5mg/kg、化合物67-1mg/kg治疗组大鼠的行走距离显著上升。

[0569] DAY14，与Model组相比，化合物67-0.3mg/kg、67-1mg/kg、67-3mg/kg治疗组大鼠的行走距离显著上升。

[0570] 大鼠五分钟直立次数实验结果显示：

[0571] DAY7及DAY14，与Model组相比，与Model组相比，直立次数无统计学差异。

[0572] 每组取5只处死后，解剖膝关节将大鼠股骨踝暴露，拍摄并观察。对大鼠膝关节股骨髁面的色泽、粗糙及完整程度进行总体观察.

[0573] 结果如图40所示：Control组大鼠的关节腔滑囊无增生情况，软骨表面光滑完整、色泽鲜亮、无纹裂；关节边缘也没有形成骨赘。而Model组可以看到大鼠关节软骨面略微粗糙，部分糜烂，有小的裂隙且色泽灰暗；关节软骨色泽丢失，表面发生虫蚀改变，边缘有骨赘形成。

[0574] 经过双氯芬酸钠和化合物67治疗后，大部分大鼠膝关节的软骨光滑鲜亮、磨损的情况显著改善。虽然也能看到部分软骨出现了轻微虫蚀的情况，但未见明显的骨赘形成。因此，化合物67可以缓解OA模型鼠膝关节软骨病变的情况。

[0575] 化合物67对OA大鼠血清细胞因子的影响如图41所示：

[0576] Model组大鼠血清中的抗炎因子IL-10水平降低。与Model组相比，双氯芬酸钠组IL-10水平显著上升，而化合物67有上调IL-10、IL-17水平的趋势。

[0577] 各组大鼠血清中的抗炎因子IL-17水平无差异。

[0578] 化合物67对OA大鼠膝关节番红固绿染色及OARSI评分的影响如图42所示：图中Control组软骨基质颜色红亮；浅层软骨和软骨下骨被固绿染成绿色。软骨结构完整，表层和中层分别为扁平状和圆形圆形的软骨细胞、深层可见软骨细胞增生。而Model组有少量番红染色褪去，局部失染；表层软骨细胞变得肿胀、数量减少、排列紊乱；潮线不规则延申、边界模糊、部分消失。

[0579] 经双氯芬酸钠和化合物67治疗后，OA模型鼠的膝骨关节有所改善，番红染色增强；软骨细胞增多、排列较规则整齐。

[0580] 接下来用OARIS评分对各组大鼠的骨关节炎严重程度进行了判断，结果如图42所示，Model组的评分比Control组显著升高，而经双氯芬酸钠和化合物67治疗后，大鼠膝骨关节炎较Model组明显要轻。而化合物67-1mg/kg、3mg/kg治疗组大鼠具有显著性，能够很好的缓解OA大鼠膝关节部位的损伤。

[0581] 本发明人利用膝关节腔内注射MIA来建立大鼠OA模型，研究化合物67对该模型大鼠的药效。发现化合物67可以改善关节损伤大鼠的行走运动能力，减缓大鼠的疼痛感。观察病变部位时，发现化合物67可以改善OA大鼠膝关节软骨磨损、侵蚀、断裂的现象。

[0582] 结论：

[0583] (1)实验结果说明化合物67治疗组大鼠的行走距离显著上升。在MIA诱导的大鼠OA模型中表现出良好的治疗效果，可以有效缓解大鼠的疼痛，改善其行走状态。

[0584] (2)大体观察结果表明，化合物67治疗组大鼠能够很好的缓解OA大鼠膝关节部位的损伤。

[0585] (3)病理切片及OARSI评分的结果表明，化合物67治疗组能够很好的缓解OA大鼠膝关节部位的损伤。

[0586] (4)Elisa结果显示，化合物67治疗组具有上调IL-10的趋势。

[0587] 综上，作为S1PR4选择性激动剂，化合物67在治疗大鼠骨关节炎模型中具有明显的药效。

[0588] 实施例10.化合物67在系统性红斑狼疮(SLE)MRL/Lpr模型小鼠中的药效评价

[0589] 采用红斑狼疮MRL/Lpr模型小鼠对化合物67进行了药效评价。

[0590] 具体分组为：MPJ control组、模型组、阳性药Cenerimod组0.5mg/kg、化合物67剂量分为1和3mg/kg两组。

[0591] 8周内体重和存活率统计结果见图43。

[0592] MAU是指尿微量白蛋白，反映肾脏异常渗漏蛋白质。MAU测定可反映早期肾病、肾损伤情况。结果显示，8周后SLE模型组小鼠尿微量白蛋白水平增高(提示肾功能损伤)，化合物67连续给药8周可明显降低小鼠尿微量白蛋白水平，作用优于Cenerimod 0.5mg/kg组(如图44所示)。

[0593] 抗双链DNA抗体(anti ds-DNA antibody(lgG))对SLE有较高的敏感性，是SLE的诊断指标以及活动性标志物。结果显示，8周后SLE模型组小鼠抗双链DNA抗体水平明显增高，化合物67连续给药8周可明显降低小鼠抗双链DNA抗体水平(如图45所示)。

[0594] 血肌酐(Serum creatinine)是一种人体肌肉代谢的产物，在肾功能正常的情况下，大部分肌酐从肾小球滤出，故可用作肾小球滤过功能的诊断和过筛指标。当肾小球滤过功能减低时，血肌酐因潴留在血液中而增高。结果显示，8周后SL

E模型组小鼠血肌酐水平明显增高，化合物67连续给药8周可明显降低小鼠血肌酐水平(如图46所示)。

[0595] 免疫学研究显示，SLE小鼠脾脏Th1、Th17细胞数量显著高于正常对照组，化合物67可显著降低Th1和Th17阳性细胞数、Th1/Th2和Th17/Treg比值，提示其治疗作用与调节T淋巴细胞的数量及功能有关(如图47所示)。

[0596] 鉴于狼疮性肾炎为SLE最常受损的器官，我们分别对各组小鼠的肾脏进行了HE和PAS染色。结果显示SLE模型组出现严重的炎性细胞浸润，系膜细胞增生，基底膜增厚，毛细血管内皮细胞增生；化合物67治疗8周后炎性细胞浸润显著减少，系膜细胞增生、基底膜增厚、毛细血管内皮细胞增生得到改善，且效果优于Cenerimod 0.5mg/kg组(如图48所示)。

[0597] 综上所述，化合物67对SLE有很好的药效，且疗效优于阳性药Cenerimod。

[0598] 实施例11.化合物30和67在强直性脊柱炎(AS)小鼠模型中的药效

[0599] 强直性脊柱炎(Ankylosing Spondylitis,AS)是一种慢性、进行性、炎症性疾病，主要影响脊柱和骶髂关节，并可能导致这些部位的疼痛和僵硬。

[0600] 1.AS小鼠模型的建立及给药方式

[0601] SKG小鼠适应性饲养后进行试验。5只小鼠作为空白对照外，其他20只小鼠在实验第0周和实验第2周腹腔注射Curdlan(3mg/只)建立AS小鼠模型，随机分为4组即模型组，阳性对照组使用阿达木单抗(10mg/kg)和化合物30(3mg/kg)及化合物67组(3mg/kg)，各组5只。给药化合物30和67组小鼠从第3.3周开始，每日灌胃给予化合物30和67，直至处死；阳性对照组腹腔注射给药阿达木单抗注射液(第3.3周第一次给药，第9周第二次给药)。每1周称量体重，以调整给药剂量。

[0602] 2.检测指标

[0603] 2.1外周临床症状

[0604] 进行四肢足趾部位的临床症状观察，对其发红、肿胀情况进行评分，共计16分(每足4分)。

[0605] 评分标准：

[0606] 0＝无肿胀

[0607] 1＝足顶部轻度肿胀和发红

[0608] 2＝足顶部严重肿胀和发红

[0609] 3＝腕关节或踝关节严重肿胀和发红

[0610] 4＝腕关节或踝关节和趾部严重肿胀。

[0611] 2.2脊柱关节病变情况

[0612] 在实验第13.4周以及实验第14.3周对小鼠进行CT扫描，获得小鼠骨骼、关节情况的影像学数据。图像WL:1400；WW：2000。

[0613] 评分标准：

[0614] 1、脊柱(共2分)：间隙变窄1分，融合得全2分。

[0615] 2、骶髂(两边各1分，共2分)：关节面模糊硬化0.5分，间隙变窄0.5分。

[0616] 3、脊柱关节突关节(两边各1分，共2分)：间隙变窄0.5分，融合得全1分。

[0617] 2.3统计学处理

[0618] 利用IBM SPSS Statistics软件进行方差分析(ANOVA)，以获得数据集的统计学结果，$P<0.05$为显著性差异。

[0619] 3.实验结果

[0620] 3.1外周临床症状

[0621] AS小鼠第4周开始出现外周炎症症状：足部红肿，趾部肿胀；耳部红肿；尾巴出现银屑、红肿等；眼部附近鼻部略脱毛、皮炎；耳部泛红。模型组小鼠症状随时间症状逐渐加重。化合物30和67组和阳性对照(阿达木单抗)组症状均弱于模型组小鼠。临床症状评分显示，与模型组比较，化合物30和67组与阳性对照(阿达木单抗)组在12周时分数显著小于模型组($P<0.05$)，结果如图49、50所示。化合物30和67组也可以明显减轻腕、踝关节肿胀(如图51所示)。

[0622] 3.2脊柱关节病变情况

[0623] CT检查结果显示，模型组小鼠有的一侧骶髂关节的关节面不清晰，且有一定损伤，上下关节突关节一侧可以观察到明显融合，另一侧间隙变窄且关节面较为模糊，脊柱部分有轻的融合现象；脊柱关节突关节间隙变窄。化合物30和67组，与阳性对照(阿达木单抗)组脊柱关节病变均弱于模型组小鼠，影像学评分显著低于模型组($P<0.05$)，结果如图52、53所示。

[0624] 结论：在强直性脊柱炎小鼠模型中，降低临床评分及减轻骨骼关节病理改变等方面化合物30和67都能达到与阳性药阿达木单抗相当甚至超越阿达木单抗的治疗效果。充分证明化合物30和67对强直性关节炎具有治疗作用。

[0625] 实施例12：化合物30和67在小鼠银屑病模型中的药效评价

[0626] Imiquimod诱导的小鼠银屑病模型是一种常用的银屑病研究模型。该模型利用外用免疫调节剂Imiquimod(IMQ)在小鼠皮肤上诱导出类似于人类银屑病的病变。

[0627] 实验材料

[0628] 小鼠：BALB/c小鼠，6-8周龄，雌性。

[0629] Imiquimod乳膏：5％的IMQ乳膏。

[0630] 实验步骤

[0631] 准备小鼠：将小鼠适应实验室环境至少一周。

[0632] 随机分组，每组一般包含5只小鼠。具体分组为注射阿达木单抗组，用于阳性对照。灌胃给药化合物30和67，分为3个剂量0.3、1和3mg/kg。

[0633] Imiquimod乳膏的涂抹(造模)：

[0634] 各组用剃刀剃除小鼠背部的毛发，面积约为2x3cm^2。

[0635] 每天涂抹5％的IMQ乳膏到小鼠背部的剃毛区域，剂量为62.5mg IMQ乳膏，持续6-7天。7天后观察小鼠皮肤反应，包括红斑、鳞屑和皮肤增厚等情况。具体实验结果如图54所示。

[0636] 在临床表现上，在咪喹莫特诱导的BALB/c雌鼠银屑病模型中，化合物30及67各浓度有显著缓解作用，且呈现剂量依赖性。其中化合物30和67在高剂量3mg/kg时药效最好，可以达到与阿达木单抗相似的治疗效果。以上结果证明化合物30和67具有治疗银屑病的潜力。

[0637] 讨论：

[0638] 发明人经过广泛而深入的研究，进而设计并合成得到了一系列未见文献报道的S1P受体调节剂小分子化合物，对得到的化合物进行了细胞水平活性测试，得到一批能够调节S1PR4和S1PR4突变蛋白的化合物，并且对活性优异的几个S1PR4

激动剂进行了体内药代动力学参数测定，发现其具有良好的口服吸收性质，具备一定的开发潜力。

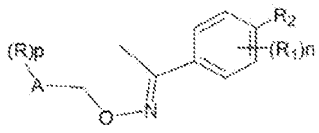
[0639] 发明人在溃疡性结肠炎、系统性红斑狼疮、骨关节炎、强直性脊柱炎等疾病模型中评价了所发明的S1PR4激动剂化合物，在多种自身免疫性疾病中都展示出体内药效，且优于S1PR1激动剂或者同靶点抗体药物。

[0640] 以上工作为由S1PR4受体介导的自身免疫性疾病的治疗奠定了基础。

[0641] 在本发明提及的所有文献都在本申请中引用作为参考，就如同每一篇文献被单独引用作为参考那样。此外应理解，在阅读了本发明的上述讲授内容之后，本领域技术人员可以对本发明作各种改动或修改，这些等价形式同样落于本申请所附权利要求书所限定的范围。

权利要求书

[权利要求 1] 式I所示的化合物、或其旋光异构体或药学上可接受的盐：



I

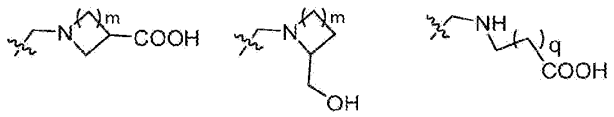
A选自取代或未取代的C_5-C_8芳环(例如苯基)或C_8-C_{14}稠芳环(例如萘基)、取代或未取代的含有1-3个选自N或O的杂原子的五元或六元杂环基；

R独立选自下组：氢、卤素、氰基、取代或未取代的C_1-C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3-C_8环烷基或环烯基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_5-C_8芳基(例如苯基)、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的C_5-C_8芳基甲酰基，p为1-3的整数；

R^1选自下组：氢、卤素、氰基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_1-C_{10}烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_6链烯基、取代或未取代的C_3-C_6环烯基、取代或未取代的C_3-C_8内酯基、取代或未取代的C_1-C_{10}酰胺基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基、取代或未取代的C_5-C_8芳杂环基；

n选自1-3整数；

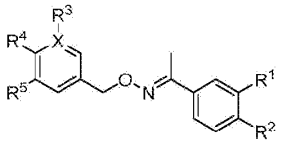
R^2选自下组：



m选自1-4整数；

q选自1-2整数。

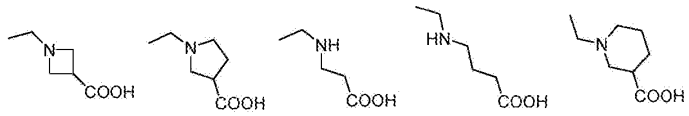
[权利要求 2] 如权利要求1所述的化合物，其特征在于，所述化合物如下式II所示，


II

式中，

R^1选自下组：氢、卤素(优选F、Cl或Br)、氰基、取代或未取代的C_1−C_5烷氧基(优选甲氧基)、取代或未取代的C_1−C_{10}烷基(优选取代或未取代的C_1−C_6烷基，例如，甲基、乙基、三氟甲基)、取代或未取代的C_3−C_8环烷基、取代或未取代的C_2−C_6链烯基、取代或未取代的C_3−C_6环烯基、取代或未取代的C_5−C_8芳基、取代或未取代的含有1−2个选自N、O或S的杂原子的五元或六元杂环基、取代或未取代的C_5−C_8芳杂环基；

R^2选自下组：



X选自：C或N；

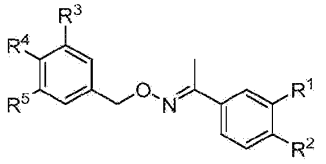
R^3不存在或是选自下组的取代基：氢、氰基、卤素、取代或未取代的C_1−C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3−C_8环烷基、氰基、取代或未取代的C_1−C_5烷氧基、取代或未取代的C_1−C_{10}烷基甲酰基、取代或未取代的C_5−C_8芳基甲酰基、取代或未取代的C_5−C_8芳基、取代或未取代的含有1−2个选自N、O或S的杂原子的五元或六元杂环基；

R^5选自下组：氢、氰基、卤素、取代或未取代的C_1−C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3−C_8环烷基、氰基、取代或未取代的C_1−C_5烷氧基、取代或未取代的C_1−C_{10}烷基甲酰基、取代或未取代的C_5−C_8芳基甲酰基、取代或未取代的C_5−

C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基；

R^4选自下组：氢、卤素、取代或未取代的C_1-C_{10}烷基、取代或未取代的C_3-C_8环烷基或环烯基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的芳基甲酰基。

[权利要求 3] 如权利要求1所述的化合物，其特征在于，所述化合物如下式Ⅲ所示，

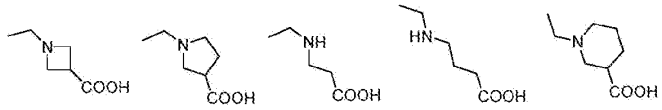


Ⅲ

式中，

R^1选自下组：氢、卤素(优选F、Cl或Br)、氰基、取代或未取代的C_1-C_5烷氧基(优选甲氧基)、取代或未取代的C_1-C_{10}烷基(优选取代或未取代的C_1-C_6烷基，例如，甲基、乙基、三氟甲基)、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_6链烯基、取代或未取代的C_3-C_6环烯基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基、取代或未取代的C_5-C_8芳杂环基；

R^2选自下组：



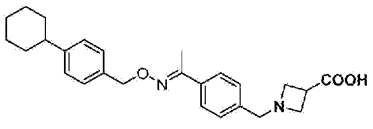
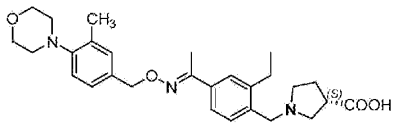
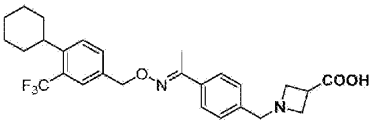
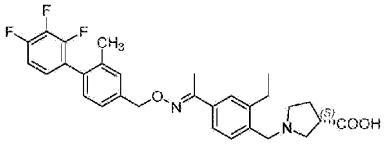
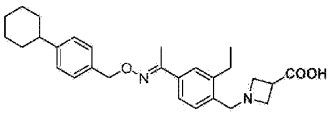
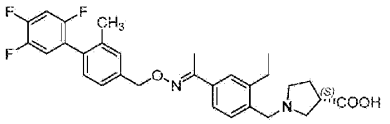
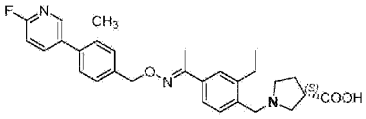
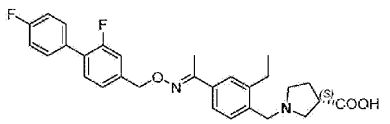
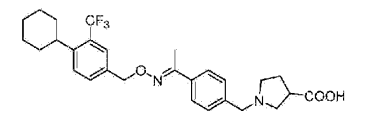
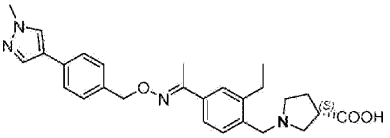
R^3选自下组的取代基：氢、氰基、卤素、取代或未取代的C_1-C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3-C_8环烷基、氰基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的C_5-C_8芳基甲酰基、取代或未取

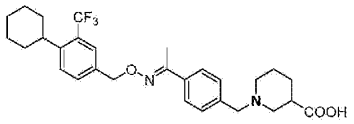
代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基；

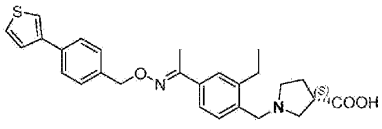
R^5选自下组：氢、氰基、卤素、取代或未取代的C_1-C_{10}烷基(例如，甲基、三氟甲基、三氟乙基)、取代或未取代的C_3-C_8环烷基、氰基、取代或未取代的C_1-C_5烷氧基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的C_5-C_8芳基甲酰基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基；

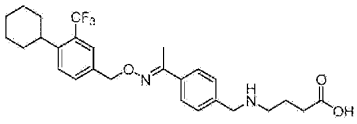
R^4选自下组：氢、卤素、取代或未取代的C_1-C_{10}烷基、取代或未取代的C_3-C_8环烷基或环烯基、取代或未取代的C_5-C_8芳基、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基、取代或未取代的C_1-C_{10}烷基甲酰基、取代或未取代的芳基甲酰基。

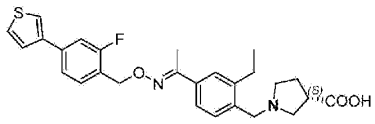
[权利要求 4] 选自下组的化合物、或其旋光异构体或药学上可接受的盐：

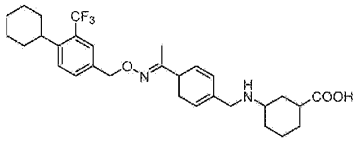











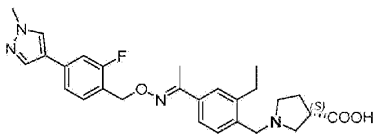


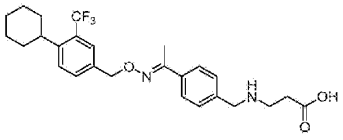


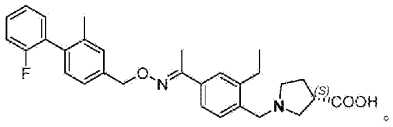


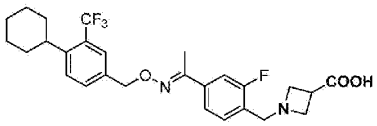


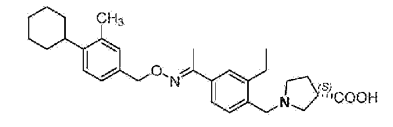




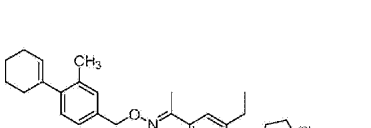


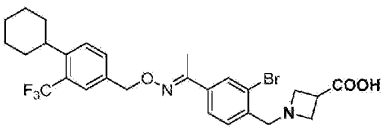


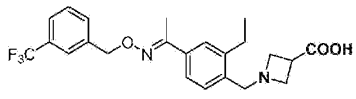


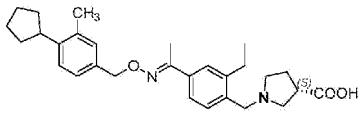


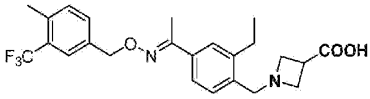


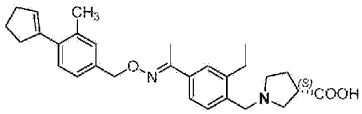


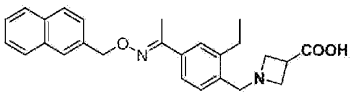


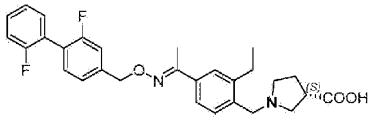


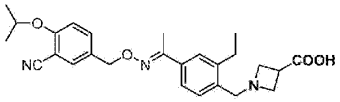


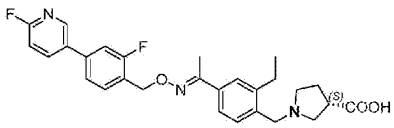


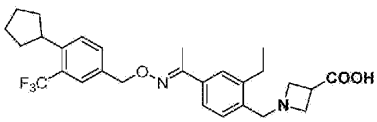


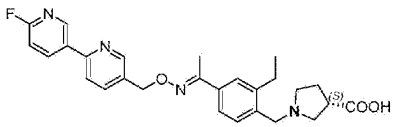


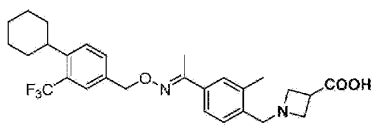


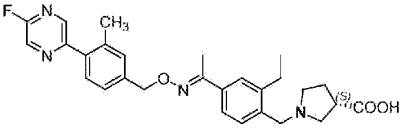


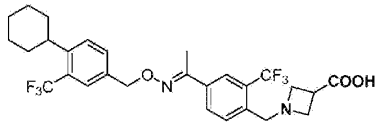
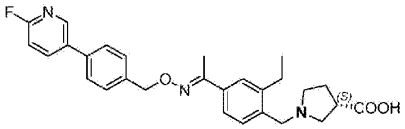
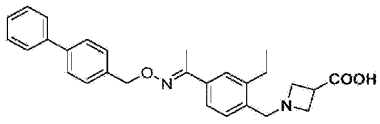
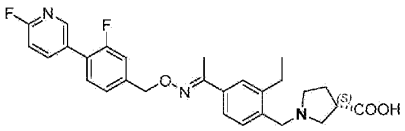
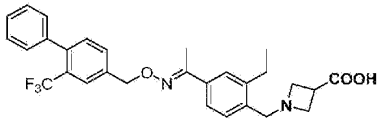
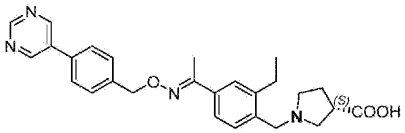
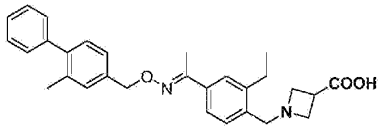
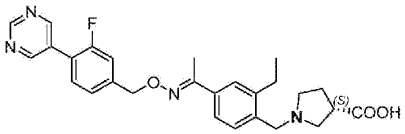
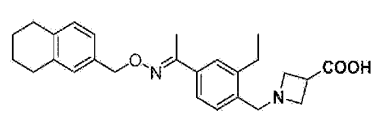
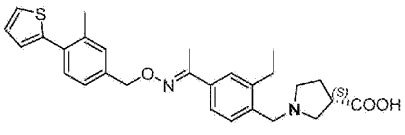
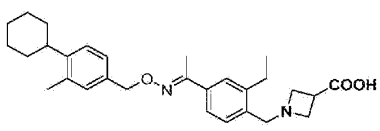


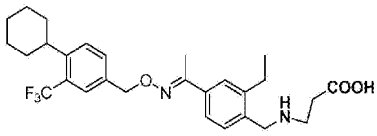


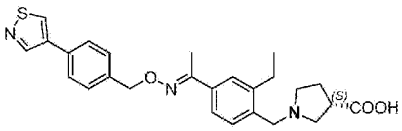


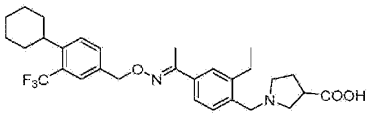


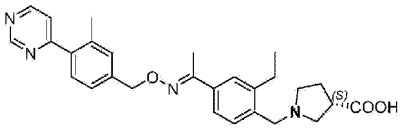


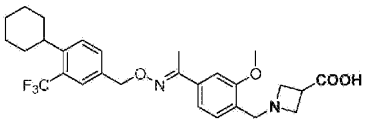












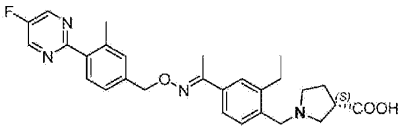


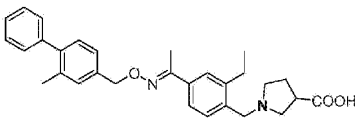


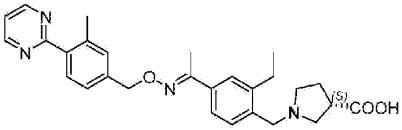


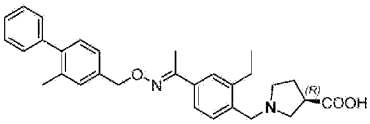


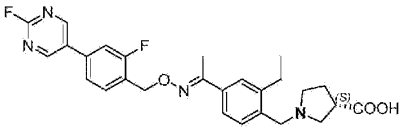


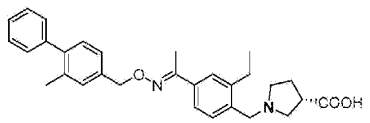


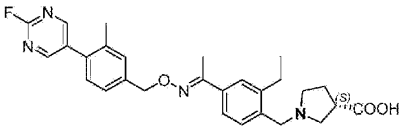


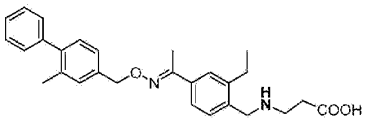


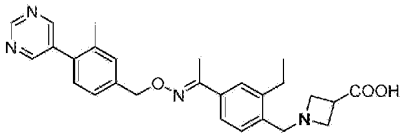


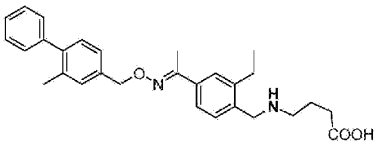


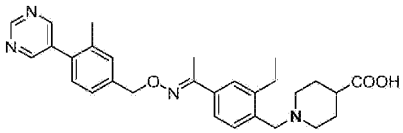


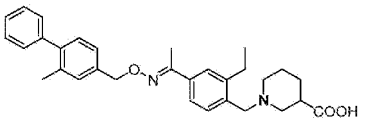


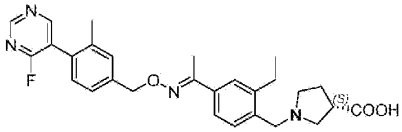


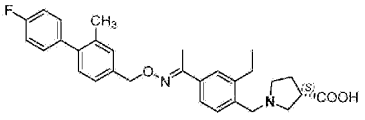


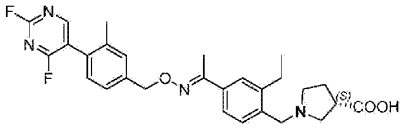


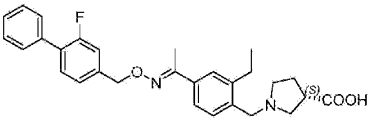


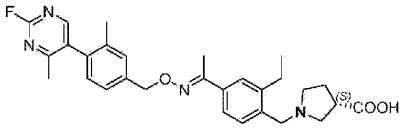


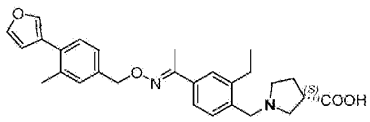


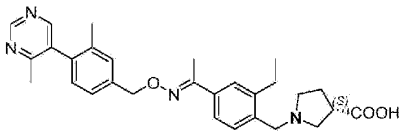


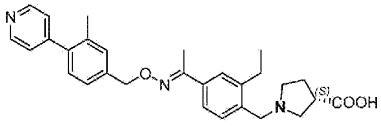
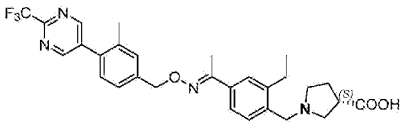
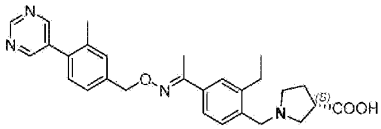
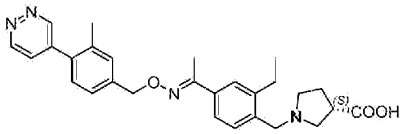
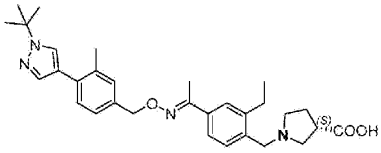
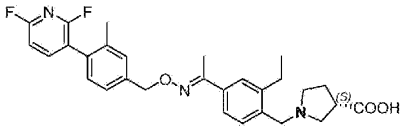
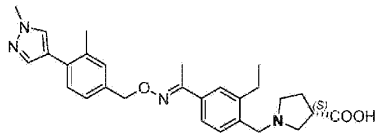
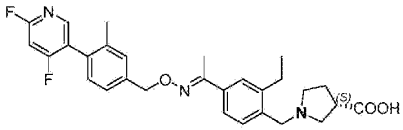
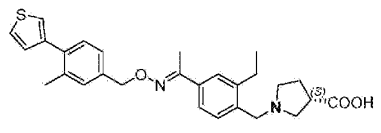
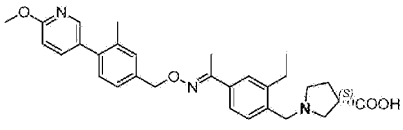
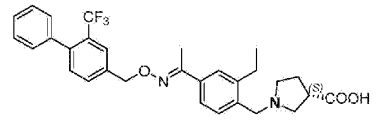
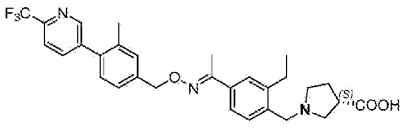


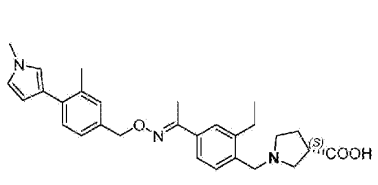
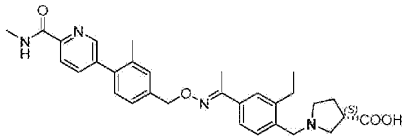
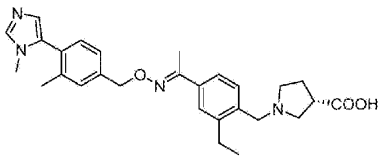
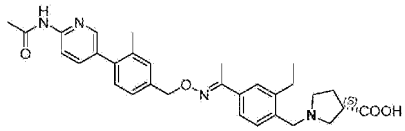
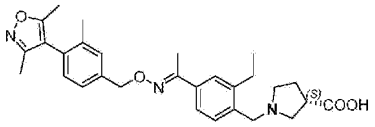
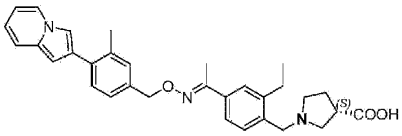
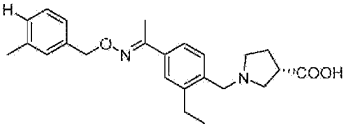
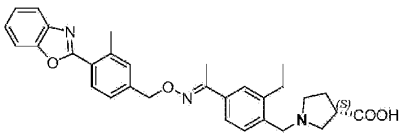
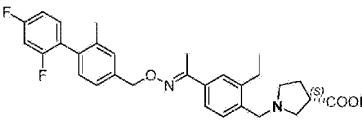
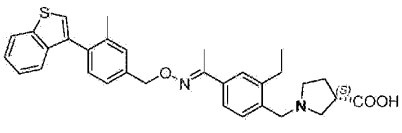
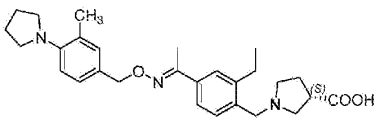


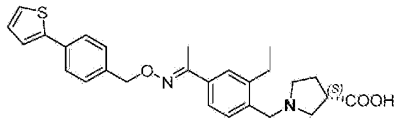


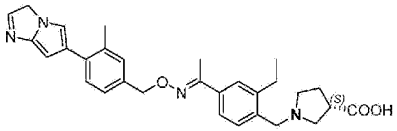


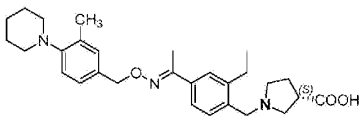


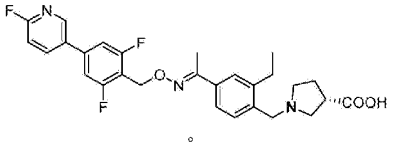













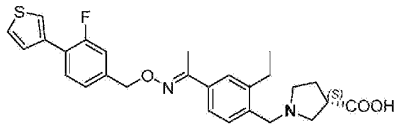












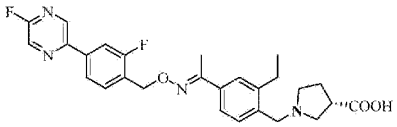


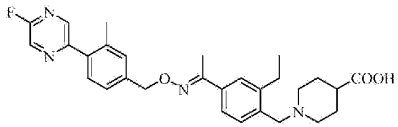


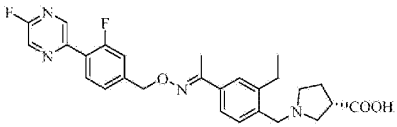


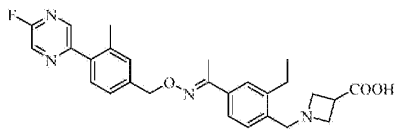


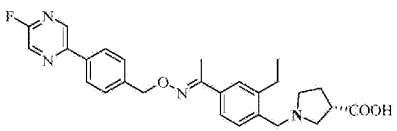


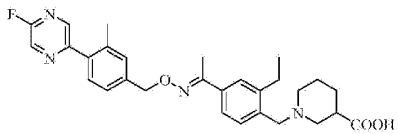


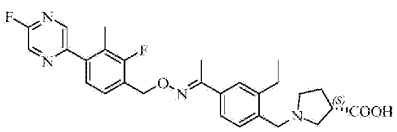


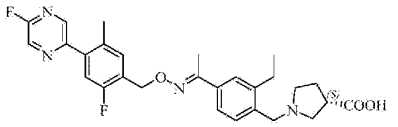


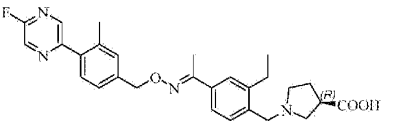


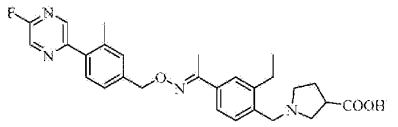


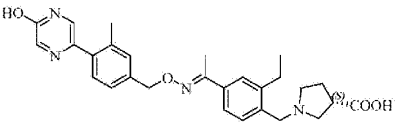








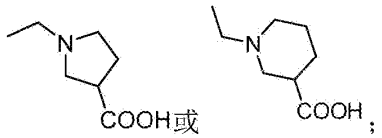




[权利要求 5] 如权利要求3所述的化合物，其特征在于，式Ⅲ中，

R^1选自下组：氢、卤素(优选F、Cl或Br)、氰基、取代或未取代的C_1-C_5烷氧基(优选甲氧基)、取代或未取代的C_1-C_6烷基(优选甲基、乙基、丙基)；

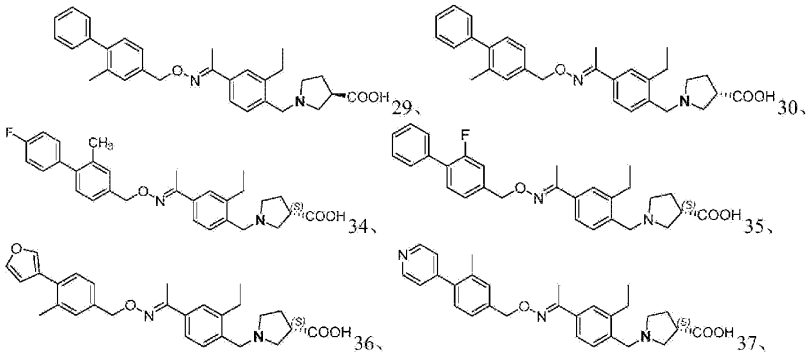
R^2为：

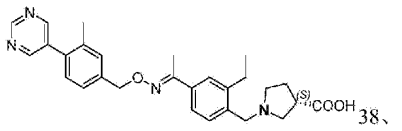


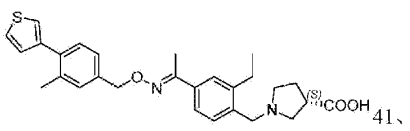
R^3和R^5独立选自下组：氢、取代或未取代的C_1-C_6烷基(优选甲基、乙基或丙基)、卤素(优选F)；

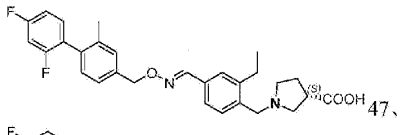
R^4选自下组：取代或未取代的C_5-C_8芳基(优选苯基或F取代的苯基)、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂环基或杂芳基。

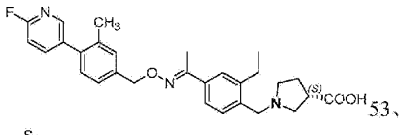
[权利要求 6] 选自下组的化合物、或其旋光异构体或药学上可接受的盐：

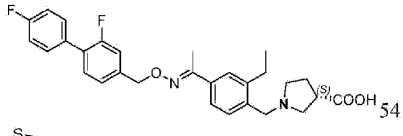


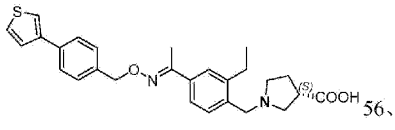

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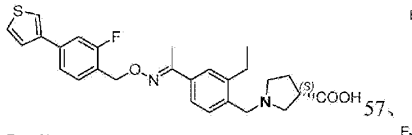

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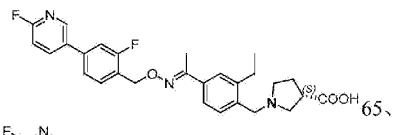

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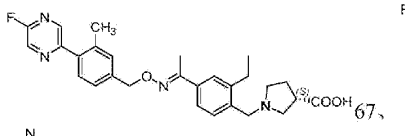

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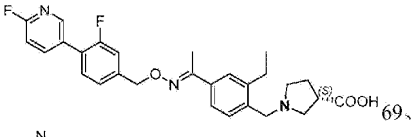

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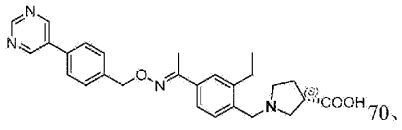

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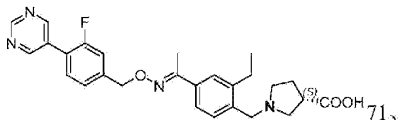

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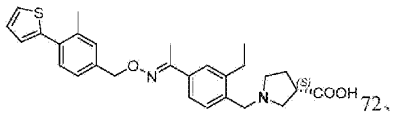

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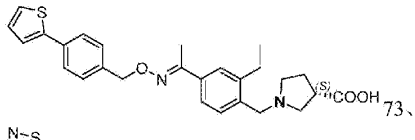

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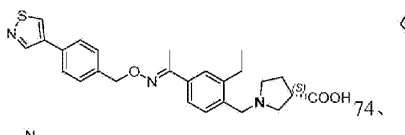

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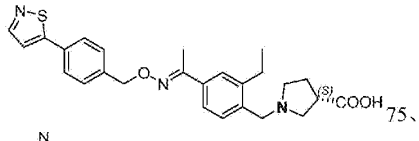

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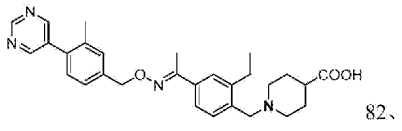

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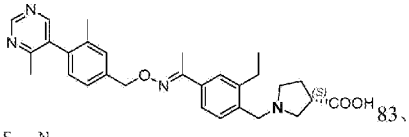

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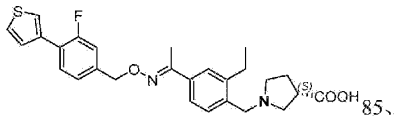

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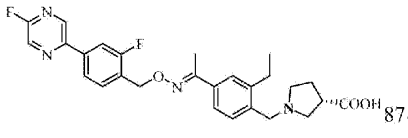

74、

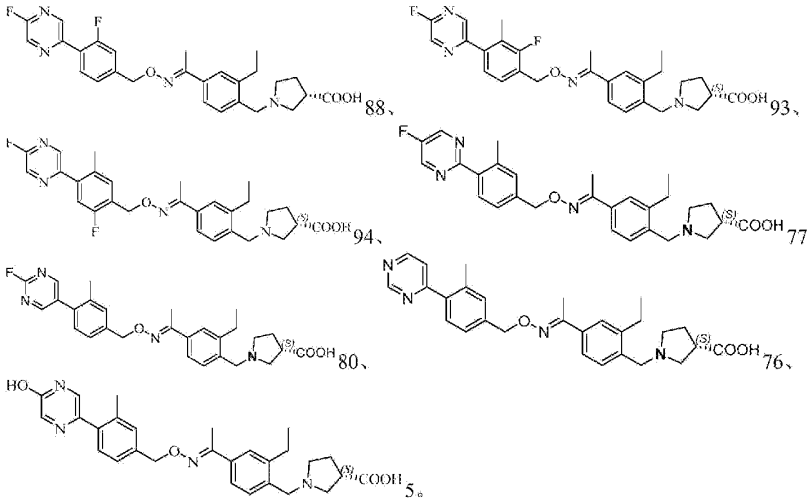

75、


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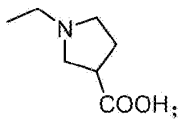

87、



[权利要求 7] 如权利要求3所述的化合物，其特征在于，式Ⅲ中，

R^1选自下组：氰基、取代或未取代的C_1-C_5烷氧基(优选甲氧基)、取代或未取代的C_1-C_6烷基(优选甲基、乙基、丙基)；

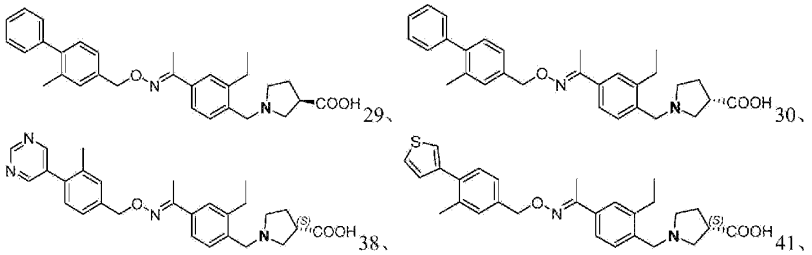
R^2为：

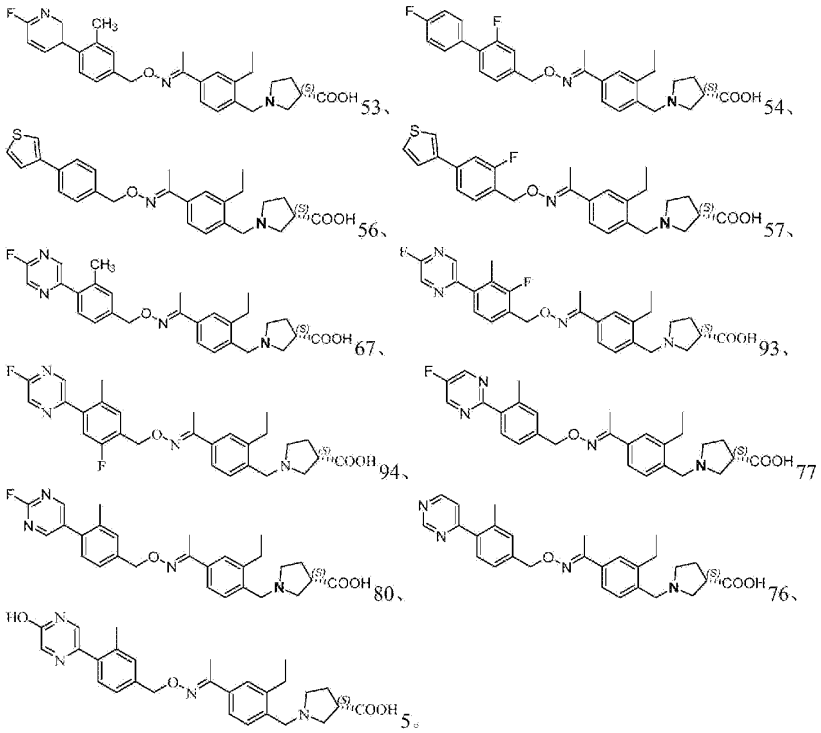


R^3和R^5独立选自下组：氢、取代或未取代的C_1-C_3烷基(优选甲基、乙基或丙基)、卤素(优选F)；

R^4选自下组：取代或未取代的C_5-C_8芳基(优选苯基或F取代的苯基)、取代或未取代的含有1-2个选自N、O或S的杂原子的五元或六元杂芳基。

[权利要求 8] 选自下组的化合物、或其旋光异构体或药学上可接受的盐：





[权利要求 9] 一种药物组合物，所述药物组合物含有权利要求1-8中任一项所述的化合物、或其旋光异构体或药学上可接受的盐，以及药学上可接受的载体或赋形剂。

[权利要求 10] 权利要求1-8中任一项所述的化合物、或其旋光异构体或药学上可接受的盐在制备S1PR调节剂中的用途，在优选的实施方式中，所述S1PR调节剂是S1PR4选择性激动剂、S1PR4突变体选择性激动剂。

[权利要求 11] 一种在受试者体内调节S1PR的方法，所述方法包括将有效量的权利要求1-8中任一项所述的化合物、或其旋光异构体或药学上可接受的盐或权利要求9所述的药物组合物给予有此需要的受试者的步骤。

[权利要求 12] 权利要求1-8中任一项所述的化合物、或其旋光异构体或药学上可接受的盐或权利要求9所述的药物组合物，用于治疗或预防S1PR4介导的疾病。

[权利要求 13] 一种包含权利要求1-8中任一项所述的化合物、或其旋光异构体或药学上可接受的盐或权利要求9所述的药物组合物，用于治疗或预防S1PR4介导的疾病的药物。